

Honorable Ronald B. Leighton

IN THE UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF WASHINGTON
AT TACOMA

STORMANS, INCORPORATED, et al.,
Plaintiffs,

vs.

MARY SELECKY, Secretary of the Washington
State Department of Health, et al.,

Defendants,

and

JUDITH BILLINGS, et al.,

Intervenors.

Civil Action No. C07-5374 RBL

**PLAINTIFFS' OFFER OF PROOF
REGARDING MECHANISM OF
ACTION OF EMERGENCY
CONTRACEPTIVES RELATED TO
THEIR RELIGIOUS BELIEFS**

Plaintiffs hereby provide their offer of proof regarding the mechanism of action of Plan B and *ella* related to their sincerely held religious beliefs. By its Amended Order Regarding Motions in Limine date March 15, 2011 (Dkt #458), the Court excluded evidence, including expert testimony, of the mechanism of action of emergency contraceptives. In its Order, the Court permitted Plaintiffs the opportunity to submit an Offer of Proof regarding the basis for their religious beliefs. The following is Plaintiffs' Offer of Proof.

PLAINTIFFS' OFFER OF PROOF REGARDING
MECHANISM OF ACTION OF EMERGENCY
CONTRACEPTIVES (C07-5374) - 1

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1 Plaintiffs' religious beliefs prevent them from taking part in the destruction of
2 innocent human life. Plaintiffs believe that a human life begins at the union of the female
3 ovum and male sperm, or fertilization, at which point the intermingling of the maternal and
4 paternal chromosomes begins. Settled science establishes that the fertilized ovum is a living,
5 human entity. (See attached report of Dr. Bruce Carlson, October 30, 2008).

6 Plaintiffs have each reviewed the attached labeling of Plan B and *ella*, FDA directives
7 regarding Plan B and *ella*, and literature regarding the debate in the medical and
8 pharmaceutical communities concerning the mechanisms of action of Plan B and *ella*, and
9 Plaintiffs firmly believe that Plan B and *ella* can prevent implantation of a fertilized ovum.

10 The manufacturer of Plan B, Barr Pharmaceutical, states in pertinent part: "It is
11 possible that Plan B may also work by preventing fertilization of an egg (the uniting of sperm
12 with the egg) or by preventing attachment (implantation) to the uterus (womb), which usually
13 occurs beginning 7 days after release of an egg from the ovary." The FDA statement on the
14 mechanism of action indicates that Plan B "may inhibit implantation (by altering the
15 endometrium)."

16 With regard to *ella*, its effective period is longer than Plan B. The manufacturer of *ella*
17 states in its labeling: "It is possible that ella may also work by preventing attachment
18 (implantation) to the uterus." The FDA states regarding the mechanism of action: "alterations
19 to the endometrium that may affect implantation may also contribute to efficacy" of *ella*.
20 Moreover, like the abortion drug RU-486, *ella* (or Ulipristal Acetate) is a selective
21 progesterone receptor modulator (SPRM) and can induce an abortion. This is because SPRM
22 works by blocking progesterone, a hormone that is necessary for pregnancy. By blocking
23 progesterone, *ella* can kill a human embryo after implantation. Notably, at the FDA advisory

1 panel meeting for *ella*, Dr. Scott Emerson, a professor of Biostatistics at the University of
 2 Washington and panelist, raised the point that the low pregnancy rate for women taking *ella*
 3 four or five days after intercourse suggests that the drug must have an abortifacient quality.
 4 (See attached report of Americans United For Life).

5 Plaintiffs' repugnance at participating in the taking of innocent human life is deeply
 6 rooted in their religious faith. The Old Testament psalmist celebrates new life in a prayer to
 7 his Creator: "You knit me together in my mother's womb, I praise you because I am fearfully
 8 and wonderfully made." Psalm 139. Human life is uniquely and inherently precious because it
 9 is created by and in the image of God himself. Genesis 2. For each Plaintiff, their conscience
 10 informed by their religious faith constrains them from participating in the ending of unborn
 11 human life.

12 Plaintiffs' conviction that human life begins to develop at the point of conception is
 13 shared by millions of Americans¹ and by leaders in the religious and scientific communities.

14 In his magisterial statement, *Evangelium vitae*, on the "Value and Inviolability of
 15 Human Life," Pope John Paul II, stated:

16
 17 Some people try to justify abortion by claiming that the result of conception, at least
 18 up to a certain number of days, cannot yet be considered a personal human life. But
 19 in fact, "from the time that the ovum is fertilized, a life is begun which is neither that
 20 of the father nor the mother; it is rather the life of a new human being with his own
 21 growth. It would never be made human if it were not human already. This has always
 been clear, and ... modern genetic science offers clear confirmation. It has
 demonstrated that from the first instant there is established the programme of what
 this living being will be: a person, this individual person with his characteristic
 aspects already well determined. Right from fertilization the adventure of a human

22 ¹ *Stenberg v. Carhart*, 530 U.S. 914, 920, 120 S.Ct. 2597 (2000) ("Millions of Americans
 23 believe that life begins at conception and consequently that an abortion is akin to causing the
 death of an innocent child; they recoil at the thought of a law that would permit it.")

1 life begins, and each of its capacities requires time-a rather lengthy time-to find its
2 place and to be in a position to act".

3 Even if the presence of a spiritual soul cannot be ascertained by empirical data, the
4 results themselves of scientific research on the human embryo provide "a valuable
5 indication for discerning by the use of reason a personal presence at the moment of
6 the first appearance of a human life: how could a human individual not be a human
7 person?"

8 Furthermore, what is at stake is so important that, from the standpoint of moral
9 obligation, the mere probability that a human person is involved would suffice to
10 justify an absolutely clear prohibition of any intervention aimed at killing a human
11 embryo. Precisely for this reason, over and above all scientific debates and those
12 philosophical affirmations to which the Magisterium has not expressly committed
13 itself, the Church has always taught and continues to teach that the result of human
14 procreation, from the first moment of its existence, must be guaranteed that
15 unconditional respect which is morally due to the human being in his or her totality
16 and unity as body and spirit: "The human being is to be respected and treated as a
17 person from the moment of conception; and therefore from that same moment his
18 rights as a person must be recognized, among which in the first place is the inviolable
19 right of every innocent human being to life²

20 Embryologists concur that the development of human beings begins with conception:

21 The development of a human being begins with fertilization, a process by which two
22 highly specialized cells, the *spermatozoon* from the male and the oocyte from the
23 female, unite to give rise to a new organism, the *zygote*. [Langman, Jan. *Medical
Embryology*. 3rd edition. Baltimore: Williams and Wilkins, 1975, p. 3]

At the moment the sperm cell of the human male meets the ovum of the female and
the union results in a fertilized ovum (zygote), a new life has begun.... The term
embryo covers the several stages of early development from conception to the ninth
or tenth week of life. [Considine, Douglas (ed.). Van Nostrand's Scientific
Encyclopedia. 5th edition. New York: Van Nostrand Reinhold Company, 1976, p.
943]

Although life is a continuous process, fertilization is a critical landmark because,
under ordinary circumstances, a new, genetically distinct human organism is thereby
formed.... The combination of 23 chromosomes present in each pronucleus results in
46 chromosomes in the zygote. Thus the diploid number is restored and the
embryonic genome is formed. The embryo now exists as a genetic unity. [O'Rahilly,

² http://www.vatican.va/holy_father/john_paul_ii/encyclicals/documents/hf_jp-ii_enc_25031995_evangelium-vitae_en.html (last viewed October 31, 2011).

1 Ronan and Müller, Fabiola. *Human Embryology & Teratology*. 2nd edition. New
2 York: Wiley-Liss, 1996, pp. 8, 29.³

3 Accordingly, Plaintiffs are constrained by their consciences from participating in the
4 taking of innocent human life which begins at conception.

5 Respectfully submitted this 31st day of October, 2011.

6
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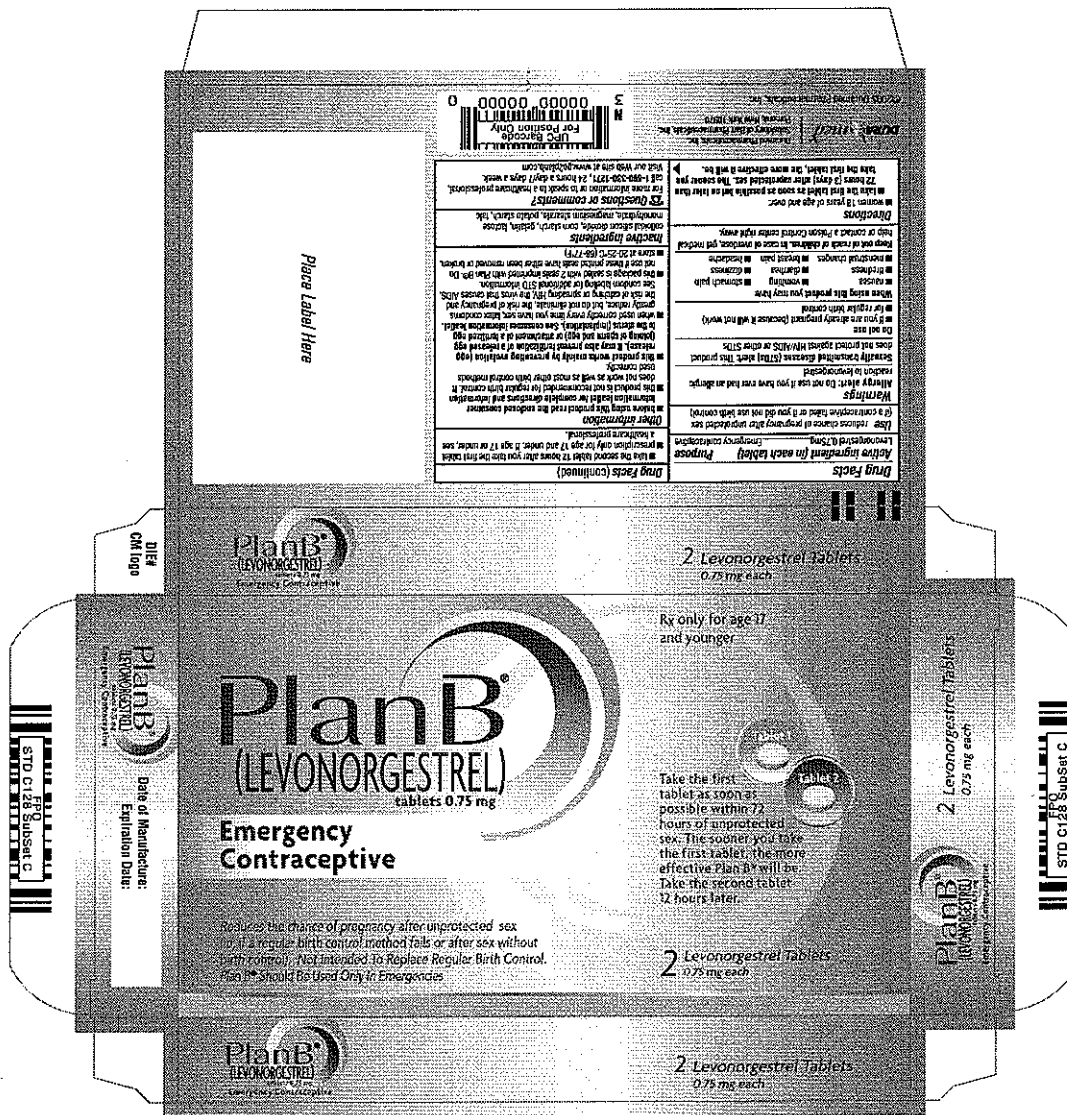
THE BECKET FUND FOR RELIGIOUS
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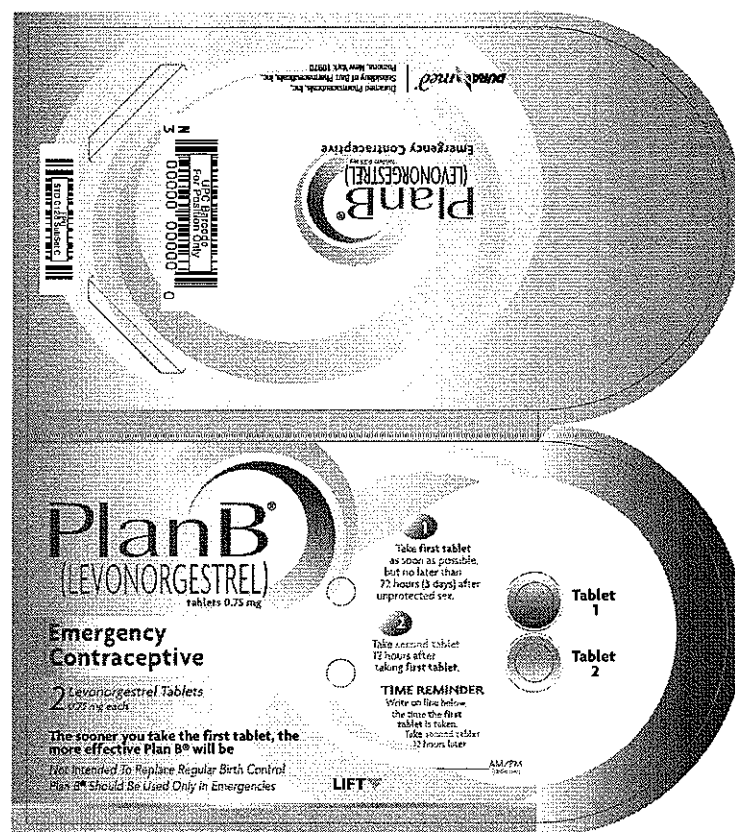
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22
23 ³ <http://www.princeton.edu/~prolife/articles/embryoquotes2.html> (last viewed October 31, 2011)



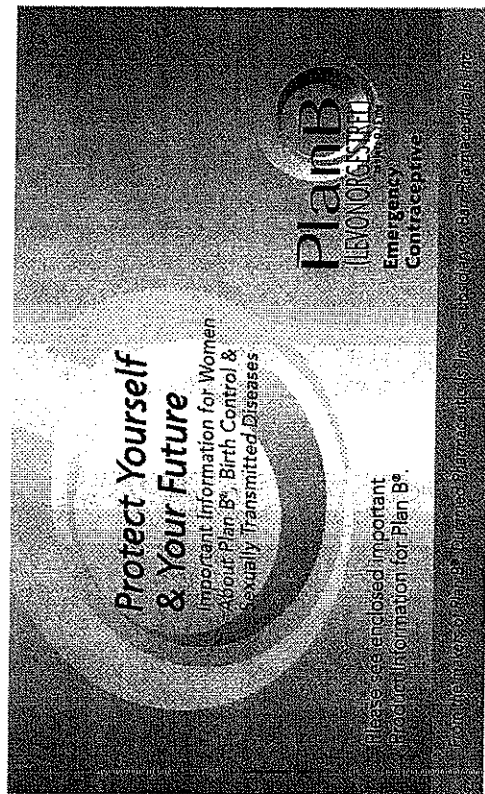
DRUG FACTS TEXT DEFINED	TYPE SIZE	TYPE FONT
• DRUG FACTS Title	9 pt	Helvetica Bold Condensed Oblique
• DRUG FACTS CONTINUED	8 pt	Helvetica Bold Cond. Oblique/Helvetica Condensed
• HEADINGS	8 pt	Helvetica Bold Condensed Oblique
• SUBHEADS/BODY TEXT	6 pt	Helvetica Bold Condensed/Helvetica Condensed
• LEADING	7 pt	
• # OF CHARACTERS PER INCH	<39	
• BULLETS	5 pt	Zapf Dingbats
• SPACE AFTER BULLETED SECTION	2 ems	
• BAR LINES, HAIR LINES	1 pt .5 pl	
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• SPACE BETWEEN HAIR LINES AND BOX END



DRUG FACTS TEXT DEFINED	TYPE SIZE	TYPE FONT
• DRUG FACTS Title	9 pt	Helvetica Bold Condensed Oblique
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• HEADINGS	8 pt	Helvetica Bold Condensed Oblique
• SUBHEADS/BOX-TEXT	6 pt	Helvetica Bold Condensed/Helvetica Condensed
• LEADINGS	7 pt	
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• BULLETS	5 pt	Zapf Dingbats
• SPACE AFTER BULLETED SECTION	2 ems	
• BAR LINES, HAIR LINES	1 pt, .5 pt	
	2 spaces	

• SPACE BETWEEN HAIR LINES AND BOX END



How does Plan B® work?

Plan B® contains a dose of the hormone levonorgestrel that is higher than in a single birth control pill. Levonorgestrel has been used in birth control pills for over 35 years. Plan B® works like a birth control pill to prevent pregnancy mainly by stopping the release of an egg from the ovary. It is possible that Plan B® may also work by preventing fertilization of an egg (the uniting of sperm with the egg) or by preventing attachment (implantation) to the uterus (womb), which usually occurs beginning 7 days after release of an egg from the ovary. Plan B® will not do anything to a fertilized egg already attached to the uterus. The pregnancy will continue.

3



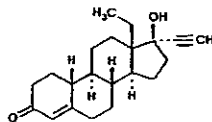
Plan B® (Levonorgestrel) Tablets, 0.75 mg

Rx only for women age 17 and younger

For women age 17 and younger, Plan B® is a prescription-only emergency contraceptive. Plan B® is intended to prevent pregnancy after known or suspected contraceptive failure or unprotected intercourse. Emergency contraceptive pills (like all oral contraceptives) do not protect against infection with HIV (the virus that causes AIDS) and other sexually transmitted diseases.

DESCRIPTION

Emergency contraceptive tablet. Each Plan B® tablet contains 0.75 mg of a single active steroid ingredient, levonorgestrel [18,19-Dinorgest-4-en-20-yn-3-one-13-ethyl-17-hydroxy-, (17 α)-(-)-], a totally synthetic progestogen. The inactive ingredients present are colloidal silicon dioxide, potato starch, gelatin, magnesium stearate, talc, corn starch, and lactose monohydrate. The structural formula is as follows:

C₂₁H₂₈O₂ Molecular Weight: 312.45**CLINICAL PHARMACOLOGY**

Emergency contraceptives are not effective if the woman is already pregnant. Plan B® is believed to act as an emergency contraceptive primarily by preventing ovulation or fertilization (by altering tubal transport of sperm and/or ova). In addition, it may inhibit implantation (by altering the endometrium). It is not effective once the process of implantation has begun.

Pharmacokinetics**Absorption**

No specific investigation of the absolute bioavailability of Plan B® in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability about 100%) and is not subject to first pass metabolism. After a single dose of Plan B® (0.75 mg) administered to 16 women under fasting conditions, maximum serum concentrations of levonorgestrel are 14.1 \pm 7.7 ng/mL (mean \pm SD) at an average of 1.6 \pm 0.7 hours. No formal study of the effect of food on the absorption of levonorgestrel has been undertaken.

Table 1: Pharmacokinetic Parameter Values Following Single Dose Administration of Plan B® (Levonorgestrel) Tablets 0.75 mg to Healthy Female Volunteers

N	Mean (\pm S.D.)					
	C _{max} (ng/mL)	T _{max} (h)	CL (L/h)	V _d (L)	T _{1/2} (h)	AUC _{0-∞} (ng/mL/h)
16	14.1 \pm 7.7	1.6 \pm 0.7	7.7 \pm 2.7	260.0	24.4 \pm 5.3	123.1 \pm 50.1

Distribution

Levonorgestrel in serum is primarily protein bound. Approximately 50% is bound to albumin and 47.5% is bound to sex hormone binding globulin (SHBG).

Metabolism

Following a single oral dosage, levonorgestrel does not appear to be extensively metabolized by the liver. The primary metabolites are 3 α ,5 β - and 3 α ,5 α -tetrahydrolevonorgestrel with 16 β -hydroxylevonorgestrel also identified. Together, these account for less than 10% of parent plasma levels. Urinary metabolites hydroxylated at the 2 α and 16 β positions have also been identified. Small amounts of the metabolites are present in plasma as sulfate and glucuronide conjugates.

Excretion

The elimination half-life of levonorgestrel following single dose administration as Plan B® (0.75 mg) is 24.4 \pm 5.3 hours. Excretion following single dose administration as emergency contraception is unknown, but based on chronic, low-dose contraceptive use, levonorgestrel and its metabolites are primarily excreted in the urine, with smaller amounts recovered in the feces.

SPECIAL POPULATIONS**Geriatric**

This product is not intended for use in geriatric (age 65 years or older) populations and pharmacokinetic data are not available for this population.

Pediatric

This product is not intended for use in pediatric (premenarcheal) populations, and pharmacokinetic data are not available for this population.

Race

No formal studies have evaluated the effect of race. However, clinical trials demonstrated a higher pregnancy rate in the Chinese population with both Plan B® and the Yuzpe regimen (another form of emergency contraception consisting of two doses of ethinyl estradiol 0.1 mg + levonorgestrel 0.5 mg). The reason for this apparent increase in the pregnancy rate of emergency contraceptives in Chinese women is unknown.

Hepatic Insufficiency and Renal Insufficiency

No formal studies have evaluated the effect of hepatic insufficiency or renal insufficiency on the disposition of emergency contraceptive tablets.

Drug-Drug Interactions

No formal studies of drug-drug interactions were conducted.

INDICATIONS & USAGE

For women age 17 and younger, Plan B® is a prescription-only emergency contraceptive that can be used to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure. To obtain optimal efficacy, the first tablet should be taken as soon as possible within 72 hours of intercourse. The second tablet must be taken 12 hours later.

Clinical Studies

A double-blind, controlled clinical trial in 1,955 evaluable women compared the efficacy and safety of Plan B® (one 0.75 mg tablet of levonorgestrel taken within 72 hours of intercourse, and one tablet taken 12 hours later) to the Yuzpe regimen (two tablets of 0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol, taken within 72 hours of intercourse, and two tablets taken 12 hours later). Plan B® was at least as effective as the Yuzpe regimen in preventing pregnancy. After a single act of intercourse, the expected pregnancy rate of 8% (with no contraception) was reduced to approximately 1% with Plan B®.

Emergency contraceptives are not as effective as routine contraception since their failure rate, while low based on a single use, would accumulate over time with repeated use (see WARNINGS). See Table 2 Below.

Table 2: Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year, United States

Method (1)	% of Women Experiencing an Unintended Pregnancy within the First Year of Use Typical Use ^a (2)	% of Women Experiencing an Unintended Pregnancy within the First Year of Use Perfect Use ^a (3)	% of Women Continuing Use at One Year ^a (4)
Coitus Interruptus ^b	85	85	
Spermicides ^c	26	6	40
Periodic Abstinence	25		63
Calendar		9	
Ovulation Method		3	
Sympto-thermal ^d		2	
Post-ovulation		1	
Withdrawal	19	4	
Cap ^e			
Parous Women	40	26	42
Nulliparous Women	26	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragm ^f	20	6	56
Condom ^g			
Female (Reality)	21	5	56
Male	14	3	61
Pill	5		71
Progestin Only		0.5	
Combined		0.1	
IUD			
Progestrone I	2.0	1.5	81
Copper T 380A	0.8	0.6	78
LN 20	0.1	0.1	81
Depo Provera	0.3	0.3	70
Norplant and Norplant-2	0.05	0.05	88
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.10	100

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.

Lactational Amenorrhea Method: LAM is a highly effective, temporary method of contraception.

Source: Trussell J. Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowal D, Guest F, Contraceptive Technology: Seventeenth Revised Edition. New York, NY: Irvington Publishers, 1998.

- Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an unintended pregnancy during the first year if they do not stop use for any other reason.
- Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly), the percentage who experience an unintended pregnancy during the first year if they do not stop use for any other reason.
- Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.
- The percentages of women becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percentage who would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.
- Foams, creams, gels, vaginal suppositories, and vaginal film.
- Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.
- With spermicidal cream or jelly.
- Without spermicides.
- The treatment schedule is one dose within 72 hours after unprotected intercourse and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral (1 dose is 2 white pills), Alesse (1 dose is 5 pink pills), Norello or Leven (1 dose is 2 light-orange pills), Lo/Ovral (1 dose is 4 white pills), Triphasil or Tri-Leven (1 dose is 4 yellow pills).
- However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches six months of age.

CONTRAINDICATIONS

Progestin-only contraceptive pills (POPs) are used as a routine method of birth control over longer periods of time, and are contraindicated in some conditions. It is not known whether these same conditions apply to the Plan B® regimen consisting of the emergency use of two progestin pills. POPs however, are not recommended for use in the following conditions:

- Known or suspected pregnancy
- Hypersensitivity to any component of the product

WARNINGS

Plan B® is not recommended for routine use as a contraceptive. Plan B® is not effective in terminating an existing pregnancy.

Effects on Menses

Menstrual bleeding patterns are often irregular among women using progestin-only oral contraceptives and in clinical studies of levonorgestrel for postcoital and emergency contraceptive use. Some women may experience spotting a few days after taking Plan B®. At the time of expected menses, approximately 75% of women using Plan B® had vaginal bleeding similar to their normal menses, 12-13% bled more than usual, and 12% bled less than usual. The majority of women (87%) had their next menstrual period at the expected time or within \pm 7 days, while 13% had a delay of more than 7 days beyond the anticipated onset of menses. If there is a delay in the onset of menses beyond 1 week, the possibility of pregnancy should be considered.

Ectopic Pregnancy

Ectopic pregnancies account for approximately 2% of reported pregnancies (19.7 per 1,000 reported pregnancies). Up to 10% of pregnancies reported in clinical studies of routine use of progestin-only contraceptives are ectopic. (over)

11001328

Revised APRIL 2008

Rx only for women age 17 and younger

(Levonorgestrel) Tablets, 0.75 mg

Plan B®

Plan B®

(Levonorgestrel) Tablets, 0.75 mg

Rx only for women age 17 and younger

Revised APRIL 2008

11001328

A history of ectopic pregnancy need not be considered a contraindication to use of this emergency contraceptive method. Health providers, however, should be alert to the possibility of an ectopic pregnancy in women who become pregnant or complain of lower abdominal pain after taking Plan B®.

PRECAUTIONS

Pregnancy

Many studies have found no effects on fetal development associated with long-term use of contraceptive doses of oral progestins (POPs). The few studies of infant growth and development that have been conducted with POPs have not demonstrated significant adverse effects.

STD/HIV

Plan B®, like progestin-only contraceptives, does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Physical Examination and Follow-up

A physical examination is not required prior to prescribing Plan B®. A follow-up physical or pelvic examination, however, is recommended if there is any doubt concerning the general health or pregnancy status of any woman after taking Plan B®.

Carbohydrate Metabolism

The effects of Plan B® on carbohydrate metabolism are unknown. Some users of progestin-only oral contraceptives (POPs) may experience slight deterioration in glucose tolerance, with increases in plasma insulin; however, women with diabetes mellitus who use POPs do not generally experience changes in their insulin requirements. Nonetheless, diabetic women should be monitored while taking Plan B®.

Drug Interactions

Theoretically, the effectiveness of low-dose progestin-only pills is reduced by hepatic enzyme-inducing drugs such as the anticonvulsants phenytoin, carbamazepine, and barbiturates, and the antituberculosis drug rifampin. No significant interaction has been found with broad-spectrum antibiotics. It is not known whether the efficacy of Plan B® would be affected by these or any other medications.

Nursing Mothers

Small amounts of progestin pass into the breast milk in women taking progestin-only pills for long-term contraception resulting in steroid levels in infant plasma of 1-6% of the levels of maternal plasma. However, no adverse effects due to progestin-only pills have been found on breastfeeding performance, either in the quality or quantity of the milk, or on the health, growth or development of the infant.

Pediatric Use

Safety and efficacy of progestin-only pills have been established in women of reproductive age for long-term contraception. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of Plan B® emergency contraception before menarche is not indicated.

Fertility Following Discontinuation

The limited available data indicate a rapid return of normal ovulation and fertility following discontinuation of progestin-only pills for emergency contraception and long-term contraception.

ADVERSE REACTIONS

The most common adverse events in the clinical trial for women receiving Plan B® included nausea (23%), abdominal pain (18%), fatigue (17%), headache (17%), and menstrual changes. The table below shows those adverse events that occurred in ≥ 5% of Plan B® users.

Table 3: Adverse Events in ≥ 5% of Women, by % Frequency

Most Common Adverse Events	Plan B® Levonorgestrel N=577 (%)
Nausea	23.1
Abdominal Pain	17.6
Fatigue	16.9
Headache	16.8
Heavier Menstrual Bleeding	13.8
Lighter Menstrual Bleeding	12.5
Dizziness	11.2
Breast Tenderness	10.7
Other complaints	9.7
Vomiting	5.6
Diarrhea	5.0

Plan B® demonstrated a superior safety profile over the Yuzpe regimen for the following adverse events:

- Nausea: Occurred in 23% of women taking Plan B® (compared to 50% with Yuzpe)
- Vomiting: Occurred in 6% of women taking Plan B® (compared to 19% with Yuzpe)

DRUG ABUSE AND DEPENDENCE

There is no information about dependence associated with the use of Plan B®.

OVERDOSAGE

There are no data on overdosage of Plan B®, although the common adverse event of nausea and its associated vomiting may be anticipated.

DOSAGE AND ADMINISTRATION

One tablet of Plan B® should be taken orally as soon as possible within 72 hours after unprotected intercourse. The second tablet should be taken 12 hours after the first dose. Efficacy is better if Plan B® is taken as directed as soon as possible after unprotected intercourse. Plan B® can be used at any time during the menstrual cycle.

The user should be instructed that if she vomits within one hour of taking either dose of medication she should contact her health care professional to discuss whether to repeat that dose.

HOW SUPPLIED

Plan B® (Levonorgestrel) Tablets, 0.75 mg are available for a single course of treatment in PVC/aluminum foil blister packages of two tablets each. The tablet is white, round and marked: INOR.

Available as:

Unit-of-use NDC 51285-769-93

Store Plan B® tablets at controlled room temperature, 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [See USP].

Mfg. by Gedeon Richter, Ltd., Budapest, Hungary
for Duramed Pharmaceuticals, Inc.
Subsidiary of Barr Pharmaceuticals, Inc.
Pomona, New York 10970
Phone: 1-800-330-1271 Website: www.go2planb.com

Revised APRIL 2008
BR-0638



ella[®]
ulipristal acetate

Watson[®]

Revised : August 2010

PATIENT INFORMATION

512890-00

**FDA Approved Patient Labeling
Patient Information
ella (el-uh)[®]
(ulipristal acetate) tablet**

Read this Patient Information Leaflet before you take **ella**. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is ella?

ella is a prescription emergency contraceptive that reduces your chance of becoming pregnant if your birth control fails or you have unprotected sex.

ella should not be used as your regular birth control. It is very important that you have a reliable form of birth control that is right for you.

ella will not protect you against HIV infection (AIDS) and other sexually transmitted diseases (STDs).

Who should not take ella?

- Do not take **ella** if you know or suspect you are already pregnant. **ella** is not for use to end an existing pregnancy. Talk to your healthcare provider before taking **ella** if you think you are pregnant.
- Do not take **ella** if you are breastfeeding, because it is not known if **ella** passes into breast milk.

What should I tell my healthcare provider before taking ella?

See "Who should not take ella?"

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Using other medicines may affect how **ella** works. These include St. John's Wort, phenytoin, rifampin, phenobarbital, and carbamazepine. Talk to your healthcare provider if you are currently using these medications.

Talk to your healthcare provider if you use hormonal birth control. Using **ella** may make your regular hormonal birth control method less effective. After using **ella**, you should use a reliable barrier method of birth control (such as a condom with spermicide) during any other times that you have sex in that same menstrual cycle.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

When is it not appropriate to use ella?

- Do not use **ella** as a regular birth control method. It does not work as well as most other forms of birth control when they are used consistently and correctly.
- Do not use **ella** if you are already pregnant.
- Do not use **ella** more than one time in the same menstrual cycle for different acts of unprotected sex or birth control failure.

How does ella work?

ella is thought to work for emergency contraception primarily by stopping or delaying the release of an egg from the ovary. It is possible that **ella** may also work by preventing attachment (implantation) to the uterus.

How should I take ella?

- Take **ella** as soon as possible within 5 days (120 hours) after unprotected sex or if you had a birth control failure.
- **ella** can be taken with or without food.
- Contact your healthcare provider right away if you vomit within 3 hours of taking **ella**. Your healthcare provider may prescribe another dose of **ella** for you.
- **ella** can be taken at any time during the menstrual cycle.

How effective is ella?

If **ella** is taken as directed, it will reduce the chance that you will get pregnant. **ella** is not effective in every case. **ella** is only to be used for a single episode of unprotected intercourse. Be sure to use a regular birth control method the next time you have sex.

ella and other emergency contraceptives may be less effective in women with a body mass index (BMI) > 30 kg/m².

What if I am already pregnant and use ella?

ella should not be taken if you are already pregnant. There is little information on whether **ella** would harm a developing baby. Contact your healthcare provider if you think you may be pregnant and have taken **ella**.

ella is not for use to terminate an existing pregnancy.


 ella
ulipristal acetate


 Watson

What should I do if my menstrual period is delayed beyond 1 week or I have severe lower stomach (abdominal) pain?

After taking ella, your next menstrual period may begin a few days earlier or later than expected. If your period is more than 7 days later than expected, you may be pregnant. You should get a pregnancy test and follow up with your healthcare provider.

If you have severe lower stomach (abdominal) pain about 3 to 5 weeks after taking ella, you may have a pregnancy outside of the uterus (womb), which is called an ectopic or tubal pregnancy. An ectopic pregnancy is a serious condition that needs medical treatment right away. Call your healthcare provider or go to the nearest emergency room right away if you think you may have an ectopic pregnancy.

How often can I use ella?

ella is meant for emergency contraception only, and is not to be used frequently or as a regular birth control. If you need to use emergency contraception often, talk to your healthcare provider and learn about methods for birth control and sexually transmitted disease prevention that are right for you.

What are the possible side effects of ella?

The most common side effects of ella include:

- headache
- nausea
- stomach (abdominal) pain
- menstrual pain (dysmenorrhea)
- tiredness
- dizziness

Some women taking ella may have their next period earlier or later than expected. If your period is more than a week late, you should get a pregnancy test.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ella. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA 1-800-FDA-1088.

How should I store ella?

- Store ella at 68-77°F (20-25°C).
- Protect ella from light. Keep ella in the blister card inside the original box until you are ready to take it.

Do not use ella if the package is torn or broken.

Keep ella and all medicines out of the reach of children.

General information about the safe and effective use of ella:

Medicines are sometimes prescribed for purposes other than those in a Patient Information Leaflet. Do not use ella for a condition for which it was not prescribed. Do not give ella to other people, even if they have the same symptoms that you have. It may harm them.

In the case of an overdose, get medical help or contact a Poison Control Center right away at 1-800-222-1222. Overdose experience with ella is limited.

This Patient Information Leaflet summarizes the most important information about ella. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about ella that is written for health professionals.

For more information, go to www.ella-rx.com or you can contact Watson Medical Communications at 1-800-272-5525.

What are the ingredients in ella?

Active ingredients: ulipristal acetate, 30 mg

Inactive ingredients: lactose monohydrate, povidone, croscarmellose sodium, and magnesium stearate

Address medical inquiries to:

WATSON
Medical Communications
P.O. Box 1953
Morristown, NJ 07962-1953
800-272-5525

Watson.

Distributed By:
Watson Pharma, Inc.
Morristown, NJ 07962 USA

Under License From:
Laboratoire HRA Pharma
75003 Paris, France

ella® is a registered trademark of
Laboratoire HRA Pharma

Manufactured By:
Osny Pharma, 95520 Osny, France; or
Leon Farma S.A., 24008 León, Spain

512890-00

ella[®]

ulipristal acetate

PHYSICIAN INFORMATION

Watson[®]

Revised: August 2010
512891-08

ella[®]
ulipristal acetate

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ella safely and effectively. See full prescribing information for ella. ella (ulipristal acetate) tablet.

Initial U.S. Approval: 2010

INDICATIONS AND USAGE

ella is a progesterone agonist/antagonist emergency contraceptive indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. ella is not intended for routine use as a contraceptive. (1)

DOSAGE AND ADMINISTRATION

One tablet taken orally as soon as possible within 120 hours (5 days) after unprotected intercourse or a known or suspected contraceptive failure. (2)

The tablet can be taken with or without food. (2)

DOSAGE FORMS AND STRENGTHS

30 mg tablet (3)

CONTRAINDICATIONS

Known or suspected pregnancy (4)

WARNINGS AND PRECAUTIONS

- ella is not indicated for termination of an existing pregnancy. Exclude pregnancy before administering. (5.1)
- Ectopic pregnancy: Women who become pregnant or complain of lower abdominal pain after taking ella should be evaluated for ectopic pregnancy. (5.2)
- Effect on menstrual cycle: ella may alter the next expected menses. If menses is delayed beyond 1 week, pregnancy should be ruled out. (5.5)
- ella does not protect against STI/HIV. (5.6)

ADVERSE REACTIONS

The most common adverse reactions ($\geq 5\%$) in the clinical trials were headache (18%), abdominal pain (12%), nausea (12%), dysmenorrhea (9%), fatigue (6%) and dizziness (5%). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Watson Laboratories, Inc. at 1-800-272-5525 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Drugs or herbal products that induce certain enzymes, such as CYP3A4, may decrease the effectiveness of ella. (7)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: ella is not recommended for use by breastfeeding women. (8.3)
- ella is not intended for use in premenarcheal (8.4) or postmenopausal women. (8.5)

See 17A for PATIENT COUNSELING INFORMATION

and FDA-Approved Patient Labeling

Revised: 08/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

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- DOSAGE AND ADMINISTRATION
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
- WARNINGS AND PRECAUTIONS
 - Existing Pregnancy
 - Ectopic Pregnancy
 - Repeated Use
 - Fertility Following Use
 - Effect on Menstrual Cycle
 - Sexually Transmitted Infections/HIV
- ADVERSE REACTIONS
 - Clinical Trials Experience
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- DRUG INTERACTIONS
 - Changes in Emergency Contraceptive Effectiveness Associated with Co-Administration of Other Products
 - Increase in Plasma Concentrations of ella Associated with Co-Administered Drugs
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 - Carcinogenesis, Mutagenesis, Impairment of Fertility
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ella is a progesterone agonist/antagonist emergency contraceptive indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. ella is not intended for routine use as a contraceptive.

2 DOSAGE AND ADMINISTRATION

Instruct patients to take one tablet orally as soon as possible within 120 hours (5 days) after unprotected intercourse or a known or suspected contraceptive failure.

The tablet can be taken with or without food.

If vomiting occurs within 3 hours of ella intake, consideration should be given to repeating the dose.

ella can be taken at any time during the menstrual cycle.

3 DOSAGE FORMS AND STRENGTHS

The ella tablet is supplied as a white to off-white, round, curved tablet containing 30 mg of ulipristal acetate and is marked "ella" on both sides.

4 CONTRAINDICATIONS

ella is contraindicated for use in the case of known or suspected pregnancy. The risks to a fetus when ella is administered to a pregnant woman are unknown. If this drug is inadvertently used during pregnancy, the woman should be apprised of the potential hazard to the fetus. [See Use in Specific Populations (8.1).]

5 WARNINGS AND PRECAUTIONS

5.1 Existing Pregnancy

ella is not indicated for termination of an existing pregnancy. Pregnancy should be excluded before prescribing ella. If pregnancy cannot be excluded on the basis of history and/or physical examination, pregnancy testing should be performed. A follow-up physical or pelvic examination is recommended if there is any doubt concerning the general health or pregnancy status of any woman after taking ella.

5.2 Ectopic Pregnancy

A history of ectopic pregnancy is not a contraindication to use of this emergency contraceptive method. Healthcare providers, however, should consider the possibility of ectopic pregnancy in women who become pregnant or complain of lower abdominal pain after taking ella. A follow-up physical or pelvic examination is recommended if there is any doubt concerning the general health or pregnancy status of any woman after taking ella.

5.3 Repeated Use

ella is for occasional use as an emergency contraceptive. It should not replace a regular method of contraception. Repeated use of ella within the same menstrual cycle is not recommended, as safety and efficacy of repeat use within the same cycle has not been evaluated.

5.4 Fertility Following Use

A rapid return of fertility is likely following treatment with ella for emergency contraception; therefore, routine contraception should be continued or initiated as soon as possible following use of ella to ensure ongoing prevention of pregnancy. While there are no data about use of ella with regular hormonal contraceptives, due to its high affinity binding to the progesterone receptor, use of ella may reduce the contraceptive action of regular hormonal contraceptive methods. Therefore, after use of ella, a reliable barrier method of contraception should be used with subsequent acts of intercourse that occur in that same menstrual cycle.

5.5 Effect on Menstrual Cycle

After ella intake, menses sometimes occur earlier or later than expected by a few days. In clinical trials, cycle length was increased by a mean of 2.5 days but returned to normal in the subsequent cycle. Seven percent of subjects reported menses occurring more than 7 days earlier than expected, and 19% reported a delay of more than 7 days. If there is a delay in the onset of expected menses beyond 1 week, rule out pregnancy.

Nine percent of women studied reported intermenstrual bleeding after use of ella.

5.6 Sexually Transmitted Infections/HIV

ella does not protect against HIV infection (AIDS) or other sexually transmitted infections (STIs).

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

ella was studied in an open-label multicenter trial (Open-Label Study) and in a comparative, randomized, single-blind, multicenter trial (Single-Blind Comparative Study). In these studies, a total of 2,637 (1,533 + 1,104) women in the 30 mg ulipristal acetate groups were included in the safety analysis. The mean age of women who received ulipristal acetate was 24.5 years and the mean body mass index (BMI) was 25.3. The racial demographics of those enrolled were 67% Caucasian, 20% Black or African American, 2% Asian, and 12% other.

The most common adverse reactions ($\geq 10\%$) in the clinical trials for women receiving ella were headache (18% overall) and nausea (12% overall) and abdominal and upper abdominal pain (12% overall). Table 1 lists those adverse reactions that were reported in $\geq 5\%$ of subjects in the clinical studies (14).

Table 1: Adverse Reactions in $\geq 5\%$ of Women (%) Receiving a Single Dose of ella (30 mg Ulipristal Acetate)

Most Common Adverse Reactions	Open-Label Study N = 1,533	Single-Blind Comparative Study N = 1,104
Headache	18	19
Nausea	12	13
Abdominal and upper abdominal pain	15	8
Dysmenorrhea	7	13
Fatigue	6	6
Dizziness	5	5

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ella:

Skin and Subcutaneous Tissue Disorders: Acne

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

No drug interaction studies have been conducted for ella in vivo. However, *in vitro* data indicate that ella is predominantly metabolized by CYP3A4.

7.1 Changes in Emergency Contraceptive Effectiveness Associated with Co-Administration of Other Products

Drugs or herbal products that induce enzymes, including CYP3A4, may decrease the plasma concentrations of ella, and may decrease its effectiveness. Some drugs or herbal products that may decrease the effectiveness of ella include:

- barbiturates
- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's Wort
- topiramate

7.2 Increase in Plasma Concentration with Co-Administered Drugs

CYP3A4 inhibitors such as itraconazole increase plasma concentrations of ella.

7.3 Effects of ella on Co-Administered

In vitro studies demonstrated that ella inhibits the activity of cytochrome P450 enzyme.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X. [See Contraindications (4).] Use of ella is contraindicated during pregnancy.

There are no adequate and well-controlled studies in women.

Ulipristal acetate was administered to pregnant rats and rabbits during the period of organogenesis. In pregnant rats, a 1/2 the human exposure, respectively area (mg/m²). There were no malformations in these studies. Adverse effect on offspring of pregnant rats administered the period of organogenesis through 1/2 the human exposure based on ulipristal acetate to pregnant monkeys trimester caused pregnancy termination; exposures 3 times the human surface area.

8.3 Nursing Mothers

It is not known if ulipristal acetate is excreted in breast milk. Because many drugs are excreted in breast milk, a breast-fed child cannot be excluded. Use of ella is not recommended.

8.4 Pediatric Use

Safety and efficacy of ella have been established in reproductive age. Safety and efficacy are not established for postpubertal adolescents less than 18 years of age. Use of ella before menarche is not recommended.

8.5 Geriatric Use

This product is not intended for use in

8.6 Race

While no formal studies have evaluated study comparison of two-pharmacokinetic exposure in South Asians may exceed African Americans. However, no difference was observed for women of different race.

8.7 Hepatic Impairment

No studies have been conducted to evaluate disease on the disposition of ella.

8.8 Renal Impairment

No studies have been conducted to evaluate disease on the disposition of ella.

10 OVERDOSAGE

Experience with ulipristal acetate overdosage study, single doses equivalent to u administered to a limited number of subjects.

11 DESCRIPTION

The ella (ulipristal acetate) tablet for oral use is a single active steroid ingredient, ulipristal (11β-(4-N,N-dimethylaminophenyl)-13,20-dione), a synthetic progesterone. Inactive ingredients are lactose monohydrate, croscarmellose sodium and magnesium stearate. Ulipristal acetate is a white to yellow crystalline solid with a molecular weight of 475.6.

*Sections or subsections omitted from the full prescribing information are not listed.

WatsonRevised: August 2010
512891-00ella[®]
ulipristal acetate**Watson****INDICATIONS**

agonist/antagonist emergency prevention of pregnancy following known or suspected contraceptive routine use as a contraceptive.

ADMINISTRATION

tablet orally as soon as possible within protected intercourse or a known failure.

or without food.
hours of ella[®] intake, consideration the dose.
during the menstrual cycle.

DESCRIPTION

a white to off-white, round, curved ulipristal acetate and is marked "ella"

in the case of known or suspected pregnancy when ella is administered to a woman. If this drug is inadvertently used in pregnancy, the potential for adverse effects should be appraised of the potential in Specific Populations (8.1).

WARNINGS

inhibition of an existing pregnancy. If used before prescribing ella, if used on the basis of history and/or pregnancy testing should be performed. A examination is recommended if there is a general health or pregnancy status of

cy is not a contraindication to use ella. Healthcare providers, possibility of ectopic pregnancy. In the case of lower abdominal pain or physical or pelvic examination any doubt concerning the general health of a woman after taking ella.

emergency contraceptive. It should be used within the same cycle as the regular hormonal contraceptive. Repeated use of ella is not recommended, as use within the same cycle has not

following treatment with ella for emergency contraception should be on as possible following use of ella. While there are no data on the use of ella in pregnancy, use of ella after use of ella, a reliable method should be used with subsequent use within the same cycle.

Cycle

sometimes occur earlier or later. In clinical trials, cycle length was not significantly different from the control group. Menstrual bleeding was reported in 19% of subjects. If there is a delay in the onset of menstruation, rule out pregnancy.

5.6 Sexually Transmitted Infections/HIV

ella does not protect against HIV infection (AIDS) or other sexually transmitted infections (STIs).

6 ADVERSE REACTIONS**6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

ella was studied in an open-label multicenter trial (Open-Label Study) and in a comparative, randomized, single-blind, multicenter trial (Single-Blind Comparative Study). In these studies, a total of 2,637 (1,533 + 1,104) women in the 30 mg ulipristal acetate groups were included in the safety analysis. The mean age of women who received ulipristal acetate was 24.5 years and the mean body mass index (BMI) was 25.3. The racial demographics of those enrolled were 67% Caucasian, 20% Black or African American, 2% Asian, and 12% other.

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Fatigue	6	6
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The following adverse reactions have been identified during post-marketing use of ella:

Skin and Subcutaneous Tissue Disorders: Acne

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

No drug interaction studies have been conducted for ella in vivo. However, *in vitro* data indicate that ella is predominantly metabolized by CYP3A4.

7.1 Changes in Emergency Contraceptive Effectiveness Associated with Co-Administration of Other Products

Drugs or herbal products that induce enzymes, including CYP3A4, may decrease the plasma concentrations of ella, and may decrease its effectiveness. Some drugs or herbal products that may decrease the effectiveness of ella include:

- barbiturates
- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's Wort
- topiramate

7.2 Increase in Plasma Concentrations of ella Associated with Co-Administered Drugs

CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma concentrations of ella.

7.3 Effects of ella on Co-Administered Drugs

In vitro studies demonstrated that ella does not induce or inhibit the activity of cytochrome P450 enzymes.

8 USE IN SPECIFIC POPULATIONS**8.1 Pregnancy**

Pregnancy Category X. [See Contraindications (4).]

Use of ella is contraindicated during an existing or suspected pregnancy.

There are no adequate and well controlled studies in pregnant women.

Ulipristal acetate was administered repeatedly to pregnant rats and rabbits during the period of organogenesis. Embryofetal loss was noted in all pregnant rats and in half of the pregnant rabbits following 12 and 13 days of dosing; at daily drug exposures 1/3 and 1/2 the human exposure, respectively, based on body surface area (mg/m^2). There were no malformations of the surviving fetuses in these studies. Adverse effects were not observed in the offspring of pregnant rats administered ulipristal acetate during the period of organogenesis through lactation at drug exposures 1/24 the human exposure based on AUC. Administration of ulipristal acetate to pregnant monkeys for 4 days during the first trimester caused pregnancy termination in 2/5 animals at daily drug exposures 3 times the human exposure based on body surface area.

8.3 Nursing Mothers

It is not known if ulipristal acetate is excreted in human milk. However, ulipristal acetate is detected in milk of lactating rats. Because many drugs are excreted in human milk, risk to the breast-fed child cannot be excluded. Use of ella by breastfeeding women is not recommended.

8.4 Pediatric Use

Safety and efficacy of ella have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents less than 18 years and for users 18 years and older. Use of ella before menarche is not indicated.

8.5 Geriatric Use

This product is not intended for use in postmenopausal women.

8.6 Race

While no formal studies have evaluated the effect of race, a cross-study comparison of two pharmacokinetic studies indicated that exposure in South Asians may exceed that in Caucasians and African Americans. However, no difference in efficacy and safety was observed for women of different races in clinical studies.

8.7 Hepatic Impairment

No studies have been conducted to evaluate the effect of hepatic disease on the disposition of ella.

8.8 Renal Impairment

No studies have been conducted to evaluate the effect of renal disease on the disposition of ella.

10 OVERDOSAGE

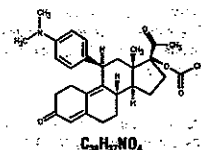
Experience with ulipristal acetate overdose is limited. In a clinical study, single doses equivalent to up to 4 times ella were administered to a limited number of subjects without any adverse reactions.

11 DESCRIPTION

The ella (ulipristal acetate) tablet for oral use contains 30 mg of a single active steroid ingredient, ulipristal acetate [17 α -acetoxy-11 β -(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione], a synthetic progesterone agonist/antagonist. The inactive ingredients are lactose monohydrate, povidone K-30, croscarmellose sodium and magnesium stearate.

Ulipristal acetate is a white to yellow crystalline powder which has a molecular weight of 475.6.

The structural formula is:

**12 CLINICAL PHARMACOLOGY****12.1 Mechanism of Action**

When taken immediately before ovulation is to occur, ella postpones follicular rupture. The likely primary mechanism of action of ulipristal acetate for emergency contraception is therefore inhibition or delay of ovulation; however, alterations to the endometrium that may affect implantation may also contribute to efficacy.

12.2 Pharmacodynamics

Ulipristal acetate is a selective progesterone receptor modulator with antagonist and partial-agonist effects at the progesterone agonist/antagonist at the progesterone receptor. It binds the human progesterone receptor and prevents progesterone from occupying its receptor.

The pharmacodynamics of ulipristal acetate depends on the timing of administration in the menstrual cycle. Administration in the mid-follicular phase causes inhibition of folliculogenesis and reduction of estradiol concentration. Administration at the time of the luteinizing hormone peak delays follicular rupture by 5 to 9 days. Dosing in the early luteal phase does not significantly delay endometrial maturation but decreases endometrial thickness by $0.6 \pm 2.2 \text{ mm}$ (mean \pm SD).

12.3 Pharmacokinetics**Absorption**

Following a single dose administration of ella in 20 women under fasting conditions, maximum plasma concentrations of ulipristal acetate and the active metabolite, monodemethyl-ulipristal acetate, were 176 and 69 ng/ml and were reached at 0.9 and 1 hour, respectively.

Figure 1: Mean (\pm SD) Plasma Concentration-time Profile of Ulipristal Acetate and Monodemethyl-Ulipristal Acetate Following Single Dose Administration of 30 mg Ulipristal Acetate

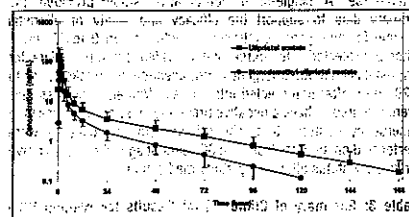


Table 2: Pharmacokinetic Parameter Values Following Administration of ella (ulipristal acetate) Tablet 30 mg to 20 Healthy Female Volunteers under Fasting Conditions

	Mean (\pm SD)				
	C_{max} (ng/ml)	AUC_{0-1} (ng·h/ml)	$AUC_{0-\infty}$ (ng·h/ml)	t_{max} (hr)	$t_{1/2}$ (hr)
Ulipristal acetate	176 (89)	548 (259)	556 (260)	0.9 (0.5-2.0)	32 (6.3)
Monodemethyl-ulipristal acetate	69 (26)	240 (59)	246 (59)	1.00 (0.8-2.0)	27 (6.9)

C_{max} = maximum concentration

AUC_{0-1} = area under the drug concentration curve from time 0 to time of last determinable concentration

$AUC_{0-\infty}$ = area under the drug concentration curve from time 0 to infinity

t_{max} = time to maximum concentration

$t_{1/2}$ = elimination half-life

* Median (range)



Effect of food: Administration of ella together with a high-fat breakfast resulted in approximately 40-45% lower mean C_{max} , a delayed t_{max} (from a median of 0.75 hours to 3 hours) and 20-25% higher mean $AUC_{0-\infty}$ of ulipristal acetate and monodemethyl-ulipristal acetate compared with administration in the fasting state. These differences are not expected to impair the efficacy or safety of ella to a clinically significant extent; therefore, ella can be taken with or without food.

Distribution

Ulipristal acetate is highly bound (> 94%) to plasma proteins, including high density lipoprotein, alpha-1-acid glycoprotein, and albumin.

Metabolism

Ulipristal acetate is metabolized to mono-demethylated and di-demethylated metabolites. *In vitro* data indicate that this is predominantly mediated by CYP3A4. The mono-demethylated metabolite is pharmacologically active.

Excretion

The terminal half-life of ulipristal acetate in plasma following a single 30 mg dose is estimated to 32.4 ± 6.3 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity: Carcinogenicity studies with ulipristal acetate have not been conducted.

Genotoxicity: Ulipristal acetate was not genotoxic in the Ames assay, *in vitro* mammalian assays utilizing mouse lymphoma cells and human peripheral blood lymphocytes, and in an *in vivo* micronucleus assay in mice.

Impairment of Fertility: Single oral doses of ulipristal acetate prevented ovulation in 50% of rats at 2 times the human exposure based on body surface area (mg/m^2). Single doses of ulipristal acetate given on post-coital days 4 or 5 prevented pregnancy in 80-100% of rats and in 50% of rabbits when given on post-coital days 5 or 6 at drug exposures 4 and 12 times the human exposure based on body surface area. Lower doses administered for 4 days to rats and rabbits were also effective at preventing ovulation and pregnancy.

14 CLINICAL STUDIES

Two multicenter clinical studies evaluated the efficacy and safety of ella. An open-label study provided the primary data to support the efficacy and safety of ulipristal acetate for emergency contraception when taken 48 to 120 hours after unprotected intercourse. A single-blind comparative study provided the primary data to support the efficacy and safety of ulipristal acetate for emergency contraception when taken 0 to 72 hours after unprotected intercourse and provided supportive data for ulipristal acetate for emergency contraception when taken > 72 to 120 hours after unprotected intercourse. Women in both studies were required to have a negative pregnancy test prior to receiving emergency contraception. The primary efficacy analyses were performed on subjects less than 36 years of age who had a known pregnancy status after taking study medication.

Table 3: Summary of Clinical Trial Results for Women Who Received a Single Dose of ella (30 mg Ulipristal Acetate)

	Open-Label Study 48 to 120 Hours*	Single-Blind Comparative Study 0 to 72 Hours*
	N = 1,242	N = 844
Expected Pregnancy Rate**	5.5	5.6
Observed Pregnancy Rate** (95% confidence interval)	2.2 (1.5, 3.2)	1.9 (1.1, 3.1)

*Time after unprotected intercourse when ella was taken

**Number of pregnancies per 100 women at risk for pregnancy

14.1 Open-Label Study

This study was a multicenter open-label trial conducted at 40 family planning clinics in the United States. Healthy women with a mean age of 24 years who requested emergency contraception 48 to 120 hours after unprotected intercourse received a dose of 30 mg ulipristal acetate (ella). The median BMI for the study subjects was 25.3 and ranged from 16.1 to 61.3 kg/m^2 .

Twenty-seven pregnancies occurred in 1,242 women aged 18 to 35 years evaluated for efficacy. The number of pregnancies expected without emergency contraception was calculated based on the timing of intercourse with regard to each woman's menstrual cycle. ella statistically significantly reduced the pregnancy rate, from an expected rate of 5.5% to an observed rate of 2.2%, when taken 48 to 120 hours after unprotected intercourse.

14.2 Single-Blind Comparative Study

This study was a multicenter, single-blind, randomized comparison of the efficacy and safety of 30 mg ulipristal acetate (ella) to levonorgestrel (another form of emergency contraception). Subjects were enrolled at 35 sites in the U.S., the United Kingdom and Ireland, with the majority (66%) having been enrolled in the U.S. Healthy women with a mean age of 26 years who requested emergency contraception within 120 hours of unprotected intercourse were enrolled and randomly allocated to receive ella or levonorgestrel 1.5 mg. The median BMI for the study subjects was 25.3 and ranged from 14.9 to 70.0 kg/m^2 .

In the ella group, 16 pregnancies occurred in 844 women aged 16 to 35 years when emergency contraception was taken 0 to 72 hours after unprotected intercourse. The number of pregnancies expected without emergency contraception was calculated based on the timing of intercourse with regard to each woman's menstrual cycle; ella statistically significantly reduced the pregnancy rate, from an expected 5.6% to an observed 1.9%, when taken within 72 hours after unprotected intercourse. There were no pregnancies observed in the women who were administered ella more than 72 hours after unprotected intercourse (10% of women who received ella).

14.3 Pooled Analysis

Data from the two studies were pooled to provide a total efficacy population of women treated with ulipristal acetate up to 120 hours after UPI. Time Trend analysis for the five 24-hour intervals from 0 to 120 hours between unprotected intercourse and treatment was conducted. There were no significant differences in the observed pregnancy rates across the five time intervals.

Subgroup analysis of the pooled data by BMI showed that for women with BMI > 30 kg/m^2 (16% of all subjects), the observed pregnancy rate was 3.1% (95% CI: 1.7, 5.7), which was not significantly reduced compared to the expected pregnancy rate of 4.5% in the absence of emergency contraception taken within 120 hours after unprotected intercourse. In the comparative study, a similar effect was seen for the comparator emergency contraception drug, levonorgestrel 1.5 mg. For levonorgestrel, when used by women with BMI > 30 kg/m^2 , the observed pregnancy rate was 7.4% (95% CI: 3.9, 13.4), compared to the expected pregnancy rate of 4.4% in the absence of emergency contraception taken within 72 hours after unprotected intercourse.

16 HOW SUPPLIED/STORAGE AND HANDLING

ella (ulipristal acetate) tablet, 30 mg is supplied in a PVC-PE-PVDC-aluminum blister. The tablet is a white to off-white, round, curved tablet marked with "ella" on both sides.

NDC 52544-238-54 (1 tablet unit of use package)

Store at 20-25°C (68-77°F). [See USP controlled room temperature.]

Keep the blister in the outer carton in order to protect from light. Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling]

Information for Patients

- Instruct patients to take ella as soon as possible and not more than 120 hours after unprotected intercourse or a known or suspected contraceptive failure.
- Advise patients that they should not take ella if they know or suspect they are pregnant and that ella is not indicated for termination of an existing pregnancy.
- Advise patients to contact their healthcare provider immediately in case of vomiting within 3 hours of taking the tablet, to discuss whether to take another tablet.
- Advise patients to seek medical attention if they experience severe lower abdominal pain 3 to 5 weeks after taking ella, in order to be evaluated for an ectopic pregnancy.
- Advise patients to contact their healthcare provider and consider the possibility of pregnancy if their period is delayed after taking ella by more than 1 week beyond the date it was expected.
- Advise patients not to use ella as routine contraception, or to use it repeatedly in the same menstrual cycle.

- Advise patients that ella may reduce the contraceptive action of regular hormonal contraceptive methods and to use a reliable barrier method of contraception after using ella, for any subsequent acts of intercourse that occur in that same menstrual cycle.
- Inform patients that ella does not protect against HIV infection (AIDS) and other sexually transmitted diseases/infections.
- Advise patients that they should not use ella if they are breastfeeding.

FDA-Approved Patient Labeling

Patient Information

ella ("el-uh")
(ulipristal acetate) tablet

Read this Patient Information Leaflet before you take ella. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is ella?

ella is a prescription emergency contraceptive that reduces your chance of becoming pregnant if your birth control fails or you have unprotected sex.

ella should not be used as your regular birth control. It is very important that you have a reliable form of birth control that is right for you.

ella will not protect you against HIV infection (AIDS) and other sexually transmitted diseases (STDs).

Who should not take ella?

- Do not take ella if you know or suspect you are already pregnant. ella is not for use to end an existing pregnancy. Talk to your healthcare provider before taking ella if you think you are pregnant.
- Do not take ella if you are breastfeeding, because it is not known if ella passes into breast milk.

What should I tell my healthcare provider before taking ella?

See "Who should not take ella?"

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Using other medicines may affect how ella works. These include St. John's Wort, phenytoin, rifampin, phenobarbital, and carbamazepine. Talk to your healthcare provider if you are currently using these medications.

Talk to your healthcare provider if you use hormonal birth control. Using ella may make your regular hormonal birth control method less effective. After using ella, you should use a reliable barrier method of birth control (such as a condom with spermicide) during any other times that you have sex in that same menstrual cycle.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

When is it not appropriate to use ella?

- Do not use ella as a regular birth control method. It does not work as well as most other forms of birth control when they are used consistently and correctly.
- Do not use ella if you are already pregnant.
- Do not use ella more than one time in the same menstrual cycle for different acts of unprotected sex or birth control failure.

How does ella work?

ella is thought to work for emergency contraception primarily by stopping or delaying the release of an egg from the ovary. It is possible that ella may also work by preventing attachment (implantation) to the uterus.

How should I take ella?

- Take ella as soon as possible within 5 days (120 hours) after unprotected sex or if you had a birth control failure.
- ella can be taken with or without food.
- Contact your healthcare provider right away if you vomit within 3 hours of taking ella. Your healthcare provider may prescribe another dose of ella for you.
- ella can be taken at any time during the menstrual cycle.

How effective is ella?

If ella is taken as directed, it will get pregnant. ella is not effective used for a single episode of unprotected sex. ella and other emergency contraceptive methods are not effective for women with a body mass index (BMI) of 30 or higher.

What if I am already pregnant or

ella should not be taken if you have information on whether ella is effective. Contact your healthcare provider if you are already pregnant and have taken ella.

ella is not for use to terminate an

What should I do if my menstrual cycle is off?

After taking ella, your next menstrual cycle may come earlier or later than expected. If you have a pregnancy test and follow up with your healthcare provider. If you have severe lower stomach pain 5 weeks after taking ella, you may have an ectopic pregnancy, which is a serious condition. Call your healthcare provider right away. Your nearest emergency room right away.

How often can I use ella?

ella is meant for emergency use only. It is not for use as a regular birth control method. Talk to your healthcare provider about methods for birth control that are right for you.

What are the possible side effects?

The most common side effects of

- headache
- nausea
- stomach (abdominal) pain
- menstrual pain (dysmenorrhea)
- tiredness
- dizziness

Some women taking ella may have a period that is earlier or later than expected. If your period is not what you expect, take a pregnancy test.

Tell your healthcare provider if you have any side effects that bother you or that does not go away.

These are not all the possible side effects. Ask your healthcare provider for more information.

Call your healthcare provider for more information. You may report side effects to FDA.

How should I store ella?

- Store ella at 68-77°F (20-25°C) in its original box until you are ready to use it.
- Do not use ella if the package is torn or damaged.
- Keep ella and all medicines out of the reach of children.

General information about the

Medicines are sometimes prescribed for conditions that were not prescribed for them. Even if they have the same name, they may harm them.

In the case of an overdose, go to the Poison Control Center right away. Your experience with ella is limited.

This Patient Information Leaflet is not a substitute for medical advice. If you have any questions about ella, ask your healthcare provider. Your healthcare provider for information about ella.

occurred in 1,242 women aged 18 to 35 years. The number of pregnancies expected after use of ella was calculated based on the data from the clinical trial. The use of ella significantly reduced the pregnancy rate, from 5.5% to an observed rate of 2.2%, when used after unprotected intercourse.

Comparative Study

In a single-blind, randomized comparison of 30 mg ulipristal acetate (ella) to a form of emergency contraception, 35 sites in the U.S., the United Kingdom and Italy (66%) having been enrolled in the study. The mean age of 25 years who requested ella within 120 hours of unprotected intercourse and randomly allocated to receive ella. The median BMI for the study subjects was 14.9 to 70.0 kg/m².

Pregnancies occurred in 844 women aged 18 to 35 years who requested ella within 120 hours of unprotected intercourse. The number of pregnancies expected after use of ella was calculated based on the data from the clinical trial. The use of ella significantly reduced the pregnancy rate, from 5.5% to an observed rate of 2.2%, when used after unprotected intercourse. There were no pregnancies in the women who were administered ella after unprotected intercourse (10% of women).

Women were pooled to provide a total efficacy of 85% with ulipristal acetate up to 120 hours after unprotected intercourse. In the comparative study, the use of ella significantly reduced the pregnancy rate, from 5.5% to an observed rate of 2.2%, when used after unprotected intercourse.

Women were pooled by BMI showed that for BMI < 30 kg/m² (16% of all subjects), the observed pregnancy rate (95% CI: 1.7, 5.7), which was not significantly different from the expected pregnancy rate of 5.5% for emergency contraception taken within 120 hours of unprotected intercourse. In the comparative study, the use of ella significantly reduced the pregnancy rate, from 5.5% to an observed rate of 2.2%, when used after unprotected intercourse.

USE AND HANDLING

ella, 30 mg is supplied in a PVC-PE-PVDC blister pack. The tablet is white to off-white, round, curved on both sides.

See USP controlled room temperature.

Keep the blister pack in order to protect from light. Store in a cool, dry place.

ADDITIONAL INFORMATION

See Labeling

ella as soon as possible and not more than 120 hours after unprotected intercourse or a known or suspected failure.

ella should not be taken if they know or suspect they are already pregnant. ella is not indicated for use in pregnancy.

ella should be taken immediately within 3 hours of taking the tablet, or within 120 hours of unprotected intercourse.

ella should be taken if they experience pain 3 to 5 weeks after taking ella, in or out of the expected period.

ella should be taken if they experience pain 3 to 5 weeks after taking ella, in or out of the expected period. ella should be taken if they experience pain 3 to 5 weeks after taking ella, in or out of the expected period.

- Advise patients that ella may reduce the contraceptive action of regular hormonal contraceptive methods and to use a reliable barrier method of contraception after using ella, for any subsequent acts of intercourse that occur in that same menstrual cycle.
- Inform patients that ella does not protect against HIV infection (AIDS) and other sexually transmitted diseases/infections.
- Advise patients that they should not use ella if they are breastfeeding.

FDA-Approved Patient Labeling Patient Information ella (ulipristal acetate) tablet

Read this Patient Information Leaflet before you take ella. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is ella?

ella is a prescription emergency contraceptive that reduces your chance of becoming pregnant if your birth control fails or you have unprotected sex.

ella should not be used as your regular birth control. It is very important that you have a reliable form of birth control that is right for you.

ella will not protect you against HIV infection (AIDS) and other sexually transmitted diseases (STDs).

Who should not take ella?

- Do not take ella if you know or suspect you are already pregnant. ella is not for use to end an existing pregnancy. Talk to your healthcare provider before taking ella if you think you are pregnant.
- Do not take ella if you are breastfeeding, because it is not known if ella passes into breast milk.

What should I tell my healthcare provider before taking ella?

See "Who should not take ella?"

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Using other medicines may affect how ella works. These include St. John's Wort, phenytoin, rifampin, phenobarbital, and carbamazepine. Talk to your healthcare provider if you are currently using these medications.

Talk to your healthcare provider if you use hormonal birth control. Using ella may make your regular hormonal birth control method less effective. After using ella, you should use a reliable barrier method of birth control (such as a condom with spermicide) during any other times that you have sex in that same menstrual cycle.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

When is it not appropriate to use ella?

- Do not use ella as a regular birth control method. It does not work as well as most other forms of birth control when they are used consistently and correctly.
- Do not use ella if you are already pregnant.
- Do not use ella more than one time in the same menstrual cycle for different acts of unprotected sex or birth control failure.

How does ella work?

ella is thought to work for emergency contraception primarily by stopping or delaying the release of an egg from the ovary. It is possible that ella may also work by preventing attachment (implantation) to the uterus.

How should I take ella?

- Take ella as soon as possible within 5 days (120 hours) after unprotected sex or if you had a birth control failure.
- ella can be taken with or without food.
- Contact your healthcare provider right away if you vomit within 3 hours of taking ella. Your healthcare provider may prescribe another dose of ella for you.
- ella can be taken at any time during the menstrual cycle.

How effective is ella?

If ella is taken as directed, it will reduce the chance that you will get pregnant. ella is not effective in every case. ella is only to be used for a single episode of unprotected intercourse. Be sure to use a regular birth control method the next time you have sex.

ella and other emergency contraceptives may be less effective in women with a body mass index (BMI) > 30 kg/m².

What if I am already pregnant and use ella?

ella should not be taken if you are already pregnant. There is little information on whether ella would harm a developing baby. Contact your healthcare provider if you think you may be pregnant and have taken ella.

ella is not for use to terminate an existing pregnancy.

What should I do if my menstrual period is delayed beyond 1 week or I have severe lower stomach (abdominal) pain?

After taking ella, your next menstrual period may begin a few days earlier or later than expected. If your period is more than 7 days later than expected, you may be pregnant. You should get a pregnancy test and follow up with your healthcare provider.

If you have severe lower stomach (abdominal) pain about 3 to 5 weeks after taking ella, you may have a pregnancy outside of the uterus (womb), which is called an ectopic or tubal pregnancy. An ectopic pregnancy is a serious condition that needs medical treatment right away. Call your healthcare provider or go to the nearest emergency room right away if you think you may have an ectopic pregnancy.

How often can I use ella?

ella is meant for emergency contraception only, and is not to be used frequently or as a regular birth control. If you need to use emergency contraception often, talk to your healthcare provider and learn about methods for birth control and sexually transmitted disease prevention that are right for you.

What are the possible side effects of ella?

The most common side effects of ella include:

- headache
- nausea
- stomach (abdominal) pain
- menstrual pain (dysmenorrhea)
- tiredness
- dizziness

Some women taking ella may have their next period earlier or later than expected. If your period is more than a week late, you should get a pregnancy test.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ella. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA 1-800-FDA-1088.

How should I store ella?

- Store ella at 68-77°F (20-25°C).
- Protect ella from light. Keep ella in the blister card inside the original box until you are ready to take it.

Do not use ella if the package is torn or broken.

Keep ella and all medicines out of the reach of children.

General information about the safe and effective use of ella:

Medicines are sometimes prescribed for purposes other than those in a Patient Information Leaflet. Do not use ella for a condition for which it was not prescribed. Do not give ella to other people, even if they have the same symptoms that you have. It may harm them.

In the case of an overdose, get medical help or contact a Poison Control Center right away at 1-800-222-1222. Overdose experience with ella is limited.

This Patient Information Leaflet summarizes the most important information about ella. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about ella that is written for health professionals.

For more information, go to www.ella-tx.com or you can contact Watson Medical Communications at 1-800-272-5525.

What are the ingredients in ella?

Active ingredients: ulipristal acetate, 30 mg

Inactive ingredients: lactose monohydrate, povidone, croscarmellose sodium, and magnesium stearate

Address medical inquiries to:

WATSON
Medical Communications
P.O. Box 1953
Morristown, NJ 07962-1953
800-272-5525

Watson.

Distributed By:
Watson Pharma, Inc.
Morristown, NJ 07962 USA

Under License From:
Laboratoire HRA Pharma
75003 Paris, France

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Laboratoire HRA Pharma

Manufactured By:
Osny Pharma, 95520 Osny, France
or
León Farma S.A., 24008 León, Spain



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October 30, 2008

Ms. Kristen Waggoner
Ellis, Li & McKinstry PLLC
601 Union Street, Suite 4900
Seattle, Washington 98011

RE: Stormans, Mesler, Thelen v. Selecky et al.
Civil Action No. C07-5374

Dear Ms. Waggoner:

I am responding to your request to provide expert testimony in the above-mentioned case, specifically in areas involving the early human embryo and in rebuttal to the expert report of David A. Grimes, M.D.

My name is Bruce M. Carlson, M.D., Ph.D., and my present position is Professor Emeritus at the University of Michigan Medical School. From 1966-2000, I was a faculty member in the Department of Anatomy and Cell Biology and served as Chairman of that Department from 1988-2000. From 2000-2004 I was Director of the Institute of Gerontology and retired as a full-time faculty member of the University in 2006. I have also served as President of the American Association of Anatomists and President of the Association of Anatomy, Cell Biology and Neurobiology Chairpersons.

My curriculum vitae is presented as Exhibit 1. I have taught human embryology at the University of Michigan Medical School for the past 42 years and among my 12 single-authored books are two widely used textbooks of embryology - Patten's Foundations of Embryology, 3rd - 6th editions and Human Embryology and Developmental Biology, 1st - 3rd editions. The fourth edition of this text is scheduled for publication in December, 2008. I have conducted and have published the results of laboratory research on vertebrate embryos and have had extensive research contact with

the Patten Human Embryo Collection at the University of Michigan and the human embryo collections residing in the National Museum of Medicine in Washington, DC, as well as human embryology collections at Charles University in Prague, Czechoslovakia.

Details of my recent involvement as an expert witness and my fee schedule are appended as Exhibits 2 and 3. Source materials for this report are listed in Exhibit 4.

The Principal Issue of This Report

A large number of people, for religious reasons, feel that upon fertilization (conception) a human embryo should be accorded the rights of and respect due to a postnatal individual. This is the belief of the plaintiffs. Fundamental to this belief are several biological issues - for example, is an embryo a living being upon fertilization of the egg and is it endowed with human qualities. These terms are very controversial because their use and the understanding of their use depend upon how they are defined. This report will approach the topic from the standpoint of biology, rather than from that of values. The principal issues to be addressed will be 1) Is the embryo living from the moment of fertilization? and 2) Is it biologically human? I shall discuss these in the context of my experience as a teacher and as a scientist who has conducted research at both ends of the life spectrum.

The Biology of the Early Human Embryo

Fertilization (Day 1). Fertilization is a series of processes, rather than a single event. In my textbooks, I have described the process of fertilization as beginning when the sperm (spermatozoon) starts to penetrate the corona radiata (a layer of cells) that surrounds the egg (ovum) and ending with the intermingling of the maternal and paternal chromosomes within 24 hours after the sperm has actually entered the egg proper. Before fertilization, both the egg and sperm are living cells, but as the result of previous meiotic divisions each contains only half the number of chromosomes (haploid number) found in a normal somatic cell within the body. If fertilization does not occur, both the

egg and the sperm will die. Fertilization normally occurs within the upper third of the uterine (fallopian) tube.

After the sperm has entered the egg, its chromosomes expand, and the proteins (protamines) that bound their genetic material become replaced with another set of similar proteins, called histones. In most normal cells, histones are involved in regulating what portions of the DNA contained within the chromosomes will or will not be able to express their genetic information, whereas protamines allow the tight packing of the chromosomes that occurs as the final shaping of the spermatozoon takes place in the testis. The mitochondria present in the spermatozoon (in the midpiece) also enter the egg, but the preponderance of evidence suggests that the DNA contained in the mitochondria does not persist in the egg in a form that will significantly affect future development of the embryo. As the chromosomes from the male begin to expand, they become contained in a cellular substructure, called the male pronucleus. While this is occurring, the chromosomes contained in the nucleus of the egg divide, and the egg gives off a presumably non-functional structure called the second polar body, which contains half of the chromosomal material that was present in the egg. The remaining female chromosomal material becomes organized into a female pronucleus. During the hours of the pronuclear stage, the DNA in both the male and female pronuclei replicates - a necessary step that anticipates the first division of the fertilized egg. Late in the first day after the sperm has penetrated the egg, the membranes that surround the male and female pronuclei break down, and the chromosomes intermingle as they undergo reorganization to form a mitotic spindle apparatus that prepares the now fertilized egg (called a zygote) to undertake a typical mitotic division. This division is completed around the end of the first day, and the embryo now consists of two cells.

With fertilization, the normal diploid number of chromosomes (46 in humans) is restored, and the genetic sex of the embryo is determined, depending upon whether the sperm carried an X or a Y chromosome. Through the previous processes of meiosis and the mingling of maternal and paternal chromosomes, the zygote is a genetically unique product. The process of fertilization also causes metabolic activation of the egg. This is necessary for cleavage and subsequent development of the embryo. The fertilized egg is a living entity, and at no time before and after fertilization did life cease to exist.

Day 2. The first few days after fertilization are called the period of cleavage, when the embryo develops from a single-celled zygote to a structure containing more than 100 cells. As an embryologist, I use the term "embryo" to refer to all stages of development after fertilization. During the second day, each of the two cells (called blastomeres) of the embryo divides, and by the end of the second day, the embryo consists of four cells.

Day 3. During the third day, the pace of cell division in the embryo accelerates, so that by the end of the third day a typical embryo may consist of as many as 16 cells. This stage is called the morula (after the Latin term for mulberry, which it resembles). The three-day embryo is still floating freely as it descends toward the uterus within the uterine tube of the mother. Toward the end of the third day a significant developmental event begins to occur. Called compaction, it is manifest by the smoothing out of the cellular boundaries at the surface of the embryo. Accompanying compaction is the emergence of different properties between the cells at the surface of the embryo and those completely embedded within the morula. Those on the surface have begun to undergo a form of specialization that commits them to becoming cells of the future placenta, as well as other structures (extraembryonic membranes) that are not part of the embryonic body. On the other hand, those on the inside remain relatively generalized, and a number of them or their descendants will ultimately form the body of the embryo.

Day 4. The fourth day sees the number of cells in the embryo increasing, and at the same time the embryo moves from the uterine tubes into the cavity of the uterus, but it is still floating freely in the fluid lining the uterine cavity. The embryo has, by now, developed a fluid-filled cavity, called a blastocoele, and the overall embryo complex is commonly called a blastocyst. The blastocyst is still surrounded by a non-cellular membrane (the zona pellucida), which surrounded the unfertilized egg. Within the zona pellucida, the blastocyst consists of an outer layer of flattened cells, called the trophoblast. These are the cells that will form the future placenta. On the inside is a mass of cells, called the inner cell mass, which will form the body of the embryo. These cells, if removed, also represent the source of embryonic stem cells. Individual cells of the inner cell mass have the potential to form any cell of the adult body.

Day 5. By the fifth day, the embryo (the blastocyst) is freely floating in the uterine cavity. It has not yet implanted into the uterine lining, but in anticipation of that event, areas of the surrounding zona pellucida are becoming degraded. Soon the blastocyst will begin to become extruded from the its zona covering in a process that is commonly referred to as "hatching." The portions of the trophoblast - the outer layer of the blastocyst - that have worked their way outside the zona are adapted to adhere to the uterine lining (the endometrium) when they come into contact with it.

Days 6-7. As the blastocyst, now freed from its zonal covering, attaches and begins to sink into the endometrial lining, its outer layer becomes more specialized into the types of cells that characterize the later placenta. In the interior, the cells of the inner cell mass are undergoing intense developmental changes, and specializations are occurring within them, as well. Among the first is the formation of a thin cellular layer that appears beneath the inner cell mass. This layer, called the hypoblast, represents the precursor of the lining of the yolk sac.

Days 8-14. This is a very important period in the history of the embryo. As the overall embryo complex continues to become embedded within the endometrium, the cells descended from the former inner cell mass undergo some very complex developmental changes in a process that is called gastrulation. This results in the formation of three layers of cells, arranged almost like a stack of three pancakes, that are specific precursors of the cells and tissues of the adult body. At this point, one can definitively identify the three body axes (anteroposterior, dorsoventral and left-right).

At What Point Does a Human Embryo Become a Human?

When an embryo should be accorded the full moral status of a postnatal individual is an issue that is based largely on a person's belief system. This question has been interpreted in a variety of ways at different times and as viewed through different lenses. Rather than repeat the litany of reasoning that would support or deny these various positions, I shall briefly discuss why individuals, such as the plaintiffs, would hold the view that upon fertilization a human embryo merits full protection.

A person may believe in the sanctity of the early human embryo because it is a tenet of that person's religion and that no further evidence is required. If this is the basis for the belief, it is not really discussable because it is based upon acceptance of the dogma of that religion. The plaintiffs' beliefs, however, are based on both religious teachings and their interpretation of scientific evidence.

Another determinant of a person's belief is that person's view of the status of the fertilized egg after examination of the biological evidence. Is it living? Is it human? Is it a separate individual? Is it unique? At what specific point does it become endowed with the human qualities in question? Many sophisticated biological and philosophical arguments have been posed on both sides of these issues, and these all merit serious consideration in appropriate venues, but more relevant in the context of this case is how these questions would likely be viewed by those who hold this belief.

There is little question about whether or not the zygote is living, because at no point has it or the precursor egg or sperm cells been biologically dead at the cellular level. There should also be no question that biologically the zygote is human (rather than some other species) in the adjectival sense. This can be easily confirmed by DNA analysis. Any further discussion of the humanity of the embryo at this or any other stage depends upon how "humanness" is defined by the participants in the discussion. In the vast majority of cases uniqueness can be confirmed through molecular technology, although experts can disagree about the finer points of this argument in cases such as identical twinning. Whether or not a zygote or an embryo of any age is separate depends largely upon one's definition of "separateness," especially in the relationship between the embryo and its mother. At no point in its life history is the human body precisely the same as it was even the previous second, and from fertilization to the time of death the human body has often been viewed as a constantly changing continuum with no discrete lines or periods of demarcation.

The concept of ensoulment at fertilization is an important one to many, despite the difficulties posed by embryo splitting or fusion. Similarly, arguments have focused upon the exact moment in the lengthy process of fertilization when ensoulment would occur. It is unlikely, however, that such arcane issues play a significant role in the reasoning of most individuals who believe that the earliest embryo deserves full protection.

Many textbooks of embryology place great emphasis on fertilization as the time when a new individual is created. For example,

1) *There is perhaps no phenomenon in the field of biology that touches so many fundamental questions as the union of the germ cells in the act of fertilization; in this supreme event all the strands of the web of two lives are gathered in one knot from which they diverge again and are rewoven in a new individual life history,... The elements that unite are single cells, each on the point of death, but by their union a rejuvenated individual is formed, which constitutes a link in the eternal processes of Life.* Lillie (1919).

2) *The time of fertilization represents the starting point in the life history, or ontogeny, of the individual.* Carlson (1996).

3) *Human development begins at fertilization when a male gamete or sperm unites with a female gamete or oocyte to form a single cell, a zygote. This highly specialized cell marks the beginning of each of us as a unique individual.* Moore and Persaud (2008).

4) *Fertilization is the process whereby two sex cells (gametes) fuse together to create a new individual with genetic potentials derived from both parents.* Gilbert (2000).

Of greatest relevance to this case, there are many reasons, biological, religious or philosophical, why individuals, such as the plaintiffs, would have cause to believe sincerely that upon fertilization a human embryo deserves full protection.

Responses to the Expert Report of Dr. David A. Grimes

In his submitted opinion of September 26, 2008, Dr. Grimes places considerable emphasis on the beginning of pregnancy, the mechanism of action of Plan B, and the assertion that Plan B cannot cause abortion. While his arguments appear to be well reasoned, in my opinion they for the most part seem to miss the point of the plaintiffs' case, namely that from the time of fertilization the human embryo deserves full protection. Specific examples will be examined below, with his paragraph numbers as reference points.

#11 Because the plaintiffs believe that human life should be protected from the time of fertilization, the discussion of pregnancy's beginning upon implantation is irrelevant, because at the time of implantation the embryo has already been worthy of protection for approximately six days.

#12 The example of in vitro fertilization is an interesting one, but not relevant here because most people, who believe in the right to life, including the plaintiffs, would view the embryo developing in vitro as morally equivalent to an unimplanted embryo in the uterine tubes or uterus. Whether or not the hypothetical woman feels that she is pregnant is not material to the main point of the plaintiffs' case. The emphasis in this paragraph is placed upon the woman and not the status of the embryo, which is the issue in question.

#13 Again, in this paragraph, Dr. Grimes' focus is on the woman, whereas that of the plaintiffs is on the rights and status of the fertilized egg.

#14 The thrust of this paragraph depends upon one's definition of conception. Standard medical dictionaries define conception as follows:

Dorland's Illustrated Medical Dictionary, 29thed. *Conception. The onset of pregnancy, marked by fertilization of an oocyte by a sperm or spermatozoon; formation of a visible zygote.*

Mosby's Medical Dictionary, 7thed. *Conception. The beginning of pregnancy, usually taken to be the instant that a spermatozoon enters an ovum and forms a viable zygote.*

Stedman's Medical Dictionary, 28thed. *Conception. Fertilization of an oocyte by a sperm.*

If one accepts the definitions of conception given in these dictionaries, Plan B, despite its common designation as an emergency contraceptive, would not be a contraceptive at all if it prevents an embryo from implanting into the uterine wall.

#15-17 Regarding the mechanism of action of Plan B, the plaintiffs' concerns would only be assuaged if the scientific evidence showed that in no case does Plan B act by preventing implantation of an existing embryo.

#18 The time of effectiveness of Plan B is best left to other experts.

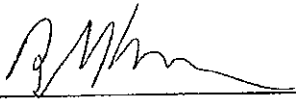
#19-22 Whether or not Plan B does or does not cause abortion depends principally upon one's definition of abortion. Of greater relevance to the plaintiffs is the question of whether or not the use of Plan B results in the ultimate destruction of living early human embryos.

#23-25 The issues discussed in these paragraphs are not germane to this discussion, but they again focus upon the woman, rather than on the embryo.

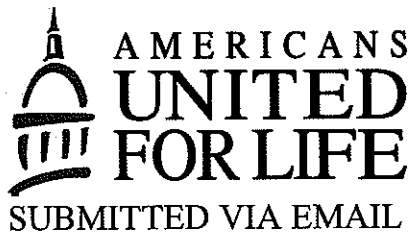
Summary

In my professional opinion, there are ample biological, religious and philosophical reasons to support the plaintiffs' sincere religious belief that the human embryo is deserving of protection upon the completion of fertilization. One may or may not agree with that position, but that is not the point of the argument.

Respectfully submitted on October 30, 2008



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Re: file code CMS-9992-IFC2

To whom it may concern:

Americans United for Life is deeply concerned about the guidelines and regulation concerning preventive services for women that was issued by the Health Resources and Services Administration (HRSA) and the Department of Health and Human Services (HHS) on August 1, 2011.

The HRSA exceeded or abused the discretion it was granted under the Affordable Care Act by mandating that insurance plans fully-cover "all Food and Drug Administration approved contraceptives, sterilization procedures..." Contrary to the stated intent of the preventive services provision of the Affordable Care Act, the HRSA mandate includes drugs and devices with known life-ending mechanisms of action, including the abortion-inducing drug *ella*.

The HRSA mandate, which will coerce the consciences of many Americans by requiring they pay for drugs and devices they have an ethical, moral, or religious objection to, was based on an ideologically-driven recommendation from the Institute of Medicine.

In addition, the “accommodation” for a narrowly-defined set of “religious employers” suggested by HHS fails to protect the conscience rights of many Americans, disrupts conscience protection laws of several states, and violates the principles of longstanding protections in federal law.

This comment addresses both the inappropriate over-reach of the HRSA mandate and the insufficiency of the conscience “accommodation” suggested by HHS.

1. The HRSA guidelines violate the intent of Section 2713(a)(4) of the Affordable Care Act by including mandated coverage for drugs and devices with life-ending mechanisms of action, such as the abortion-inducing drug *ella*.

The statutory language of Section 2713(a)(4), which was added to the Affordable Care Act¹ by amendment on December 3, 2009 and requires private insurance plans to cover certain preventive services, does not require the inclusion of “contraception” as a covered service. Further, statements offered by the amendment’s author as well as statements offered during the Senate floor debate over the addition of Section 2713(a)(4) to the Act demonstrate that the amendment was intended to prevent *diseases*, not to end pregnancies. Specifically, abortion was not intended to be included under the amendment “in any way.” Thus, the legislative history of the amendment suggests that by mandating coverage for “all Food and Drug Administration (FDA) approved contraceptives,” which includes the abortion-inducing drug *ella*, the HRSA abused or exceeded its discretion.

a. Section 2713(a)(4) of the Affordable Care Act does not explicitly include contraception, and the Senate floor debate over the addition of Section 2713(a)(4) to the Act demonstrates that it the amendment was intended to prevent *diseases*, not to end pregnancies.

Senator Barbara Mikulsi (D-MD), who offered the amendment which became Section 2713(a)(4) of the Affordable Care Act, issued a press release providing the following description of her amendment:

Services that would be covered under the Mikulski Amendment are likely to include cervical cancer screenings for a broad group of women; annual mammograms for women under 50; pregnancy and

¹ Pub. L. 111-148 (2010) [hereinafter ACA].

postpartum depression screenings; screenings for domestic violence; and annual women's health screenings, which would include testing for diseases that are leading causes of death for women such as heart disease and diabetes.²

In her prepared floor statement, Senator Mikulski again emphasized that her amendment was meant to cover life-saving, disease-preventing services, concluding:

Often health care doesn't cover basic women's health care like mammograms and cervical cancer screenings. My amendment is about saving lives and saving money to give women access to comprehensive preventive services that are affordable and life saving.³

Further, during a debate over the amendment on the Senate Floor on December 3, 2009, Senator Mikulski had the following exchange with Senator Robert Casey (D-PA) in which she clarified that abortion was not intended to be covered "in any way" and, in fact, her amendment was "strictly concerned with ensuring that women get the kind of preventive screenings and treatments they need to **prevent diseases** particular to women..." (emphasis added):

Mr. CASEY. There is one clarification I would like to ask the Senator. I know we discussed it during the HELP markup and it was not clarified at that time and thus I chose to vote against the amendment because of the possibility that it might be construed so broadly as to cover abortion. But I understand that the Senator has now clarified specifically that this amendment will not cover abortion in any way. Specifically, abortion has never been defined as a preventive service and there is neither legislative intent nor the language in this amendment to cover abortion as a preventive service or to mandate abortion coverage in any way. I ask the Senator is that correct?

Ms. MIKULSKI. Yes, that is correct. This amendment does not cover abortion. Abortion has never been defined as a preventive

² Press Release, Senator Barbara Mikulski, Mikulski Puts Women First in Health Care Debate (November 30, 2009), *available at* <http://mikulski.senate.gov/media/record.cfm?id=320304> (*last visited* Sept. 20, 2011).

³ *Id.*

service. This amendment is strictly concerned with ensuring that women get the kind of preventive screenings and treatments they need to prevent diseases particular to women such as breast cancer and cervical cancer. There is neither legislative intent nor legislative language that would cover abortion under this amendment, nor would abortion coverage be mandated in any way by the Secretary of Health and Human Services.⁴

First, pregnancy is not a disease and it is, thus, illogical to include elective contraceptive-coverage through an amendment “strictly concerned” with preventing diseases. Moreover, it is directly contrary to Senator Mikulski’s assurance that abortion would not be covered “in any way” to include abortion-inducing drugs, such as *ella*, in preventive care and screenings.

- b. Contrary to the stated intent of Section 2713(a)(4), HRSA’s mandated coverage for the “all FDA-approved contraceptives” inappropriately includes drugs and devices with known life-ending mechanisms of action, including the abortion-inducing drug *ella*.**

The guidelines issued by the HRSA mandating coverage for contraceptives clarifies that its definition is broad: “All Food and Drug Administration approved contraceptive methods, sterilization procedures, and patient education and counseling for all women with reproductive capacity.” Such a definition includes drugs and devices with known life-ending mechanisms of action, including the abortion-inducing drug *ella*.

Like the abortion drug RU-486, Ulipristal Acetate (*ella*) is a selective progesterone receptor modulator (SPRM). Despite its “indication” for use as “emergency contraception,” *ella* – like RU-486 – can induce an abortion.⁵ This is because an

⁴ Cong. Rec. S12274 (daily ed. Dec. 3, 2009) (colloquy between Sen. Mikulski and Sen. Casey), available at <http://thomas.loc.gov>. On December 1, 2009, Senator Mikulski stated: “There are no abortion services included in the Mikulski amendment. It is screening for diseases that are the biggest killers for women – the silent killers of women. It also provides family planning – but family planning as recognized by other acts.” Cong. Rec. S12028 (daily ed. Dec. 1, 2009) (statement of Senator Mikulski), available at <http://thomas.loc.gov>.

⁵ “The mechanism of action of ulipristal in human ovarian and endometrial tissue is identical to that of its parent compound mifepristone.” D. Harrison & J. Mitroka, *Defining Reality: The Potential Role of Pharmacists in Assessing the Impact of Progesterone Receptor Modulators and Misoprostol in Reproductive Health*, 45 *Annals Pharmacotherapy* 115 (Jan. 2011).

SPRM “works” by blocking progesterone, a hormone that is necessary for pregnancy.⁶ By blocking progesterone, *ella* can kill a human embryo even after implantation.

Studies confirm that *ella* is harmful to an embryo.⁷ The FDA’s own labeling notes that *ella* may “affect implantation,”⁸ and contraindicates (or advises against) use of *ella* in the case of known or suspected pregnancy. Notably, at the FDA advisory panel meeting for *ella*, Dr. Scott Emerson, a professor of Biostatistics at the University of Washington and panelist, raised the point that the low pregnancy rate for women taking *ella* four or five days after intercourse suggests that the drug *must* have an “abortifacient” quality.⁹

⁶ Planned Parenthood materials acknowledge that chemical abortions are accomplished by blocking progesterone. See e.g. Planned Parenthood of Arizona, Client Information for Informed Consent: using the abortion pill, available at [http://www.plannedparenthood.org/ppaz/images/Arizona/web-AB_by_Pill_E\(1\).pdf](http://www.plannedparenthood.org/ppaz/images/Arizona/web-AB_by_Pill_E(1).pdf) (last visited Sept. 1, 2011). (“Abortion pill” is a popular name for a medicine called mifepristone....It ends the pregnancy. It does this by keeping your body from making a certain hormone called progesterone. The pregnancy cannot go on without progesterone.”)

⁷ See European Medicines Agency, Evaluation of Medicines for Human Use: CHMP Assessment Report for Ellaone 16 (2009), available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001027/WC500023673.pdf (last visited Sept. 27, 2011). See also *ella* Labeling Information (Aug. 13, 2010), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022474s000lbl.pdf (last visited Sept. 27, 2011).

⁸ *ella* Labeling Information (Aug. 13, 2010), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022474s000lbl.pdf (last visited Sept. 27, 2011).

⁹ See Transcript, Food and Drug Administration Center for Drug Evaluation and Research (CDER), Advisory Committee for Reproductive Health Drugs, June 17, 2010, available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM218560.pdf> (last visited Sept. 26, 2011). “What’s very, very bothersome here, again, to me, is that we shouldn’t be seeing this much of an effect according to your presumed mechanisms of action; that if there is no abortifacient aspect of this treatment, no effect on implantation, I just can’t make these numbers jive, unless there is a substantial difference in the demographics according to the women who are presenting with this sort of data. ...” “So this still comes back to this mechanism of action then. Why would we expect that if -- and I’ll even concede that the primary mechanism of action might be delayed ovulation, but not in this group that’s five days out from unprotected intercourse.”

The response to Dr. Emerson’s questions given by Dr. Erin Gainer, representing HRA Pharma, *ella*’s sponsor, acknowledged that HRA Pharma lacked sufficient data to make an assurance that *ella* did not have an abortifacient aspect, “Again, given the variability that we know when ovulation actually occurs in a given cycle, it’s very hard to comment on how many of the women treated days 4 and 5 may have been post-ovulation. We don’t have biochemical data on the

Other FDA-labeled “contraceptives” also have known life-ending mechanisms of action. Plan B, commonly referred to as “the morning after pill,” can kill a human embryo by preventing implantation.¹⁰ Intrauterine Devices (IUDs) are also acknowledged to work not only by preventing conception, but by blocking implantation.¹¹ Other hormonal contraceptives are also argued to change the endometrial lining making a woman’s uterus “hostile” for the implantation of a human embryo.¹² The more “effective” a contraceptive drug or device is generally coincides with a mechanism of action other than preventing conception.

Notably, *ella*’s deadliness goes beyond that of any other “contraceptive” approved at the time of the Affordable Care Act’s enactment. Without diminishing the legitimate and serious objections to the deceptive approval of other life-ending drugs and devices, it should be acknowledged that by approving *ella* as “contraception” the FDA has removed, not simply blurred, the line between “contraception” and “abortion” drugs. No longer is the FDA hiding behind a changed definition of pregnancy¹³; the FDA-approved “contraceptive” *ella* can work by ending an “established” pregnancy.

individual women included. So it is very hard to comment on where those women actually were.”

¹⁰ Plan B Approved Labeling, *available at*

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021045s011_Plan_B_PRNTLBL.pdf (last visited Sept. 27, 2011). The FDA’s labeling acknowledges that Plan B can prevent implantation of a human embryo.

¹¹ See <http://www.womenshealth.gov/publications/our-publications/fact-sheet/birth-control-methods.pdf> (last visited Sept. 27, 2011). The Department of Health and Human Services guide to “Birth Control Methods” describes among the mechanisms of action for copper IUDs, “If fertilization does occur, the IUD keeps the fertilized egg from implanting in the lining of the uterus.” For hormonal IUDs the guide states, “It also affects the ability of a fertilized egg to successfully implant in the uterus.”

¹² See e.g. Frye, *An Overview of oral contraceptives: Mechanisms of action and clinical use*, 66 *Neurology* S29 (2006). “[C]hanges in the endometrium may affect survival of a blastocyst within the uterus or prevent implantation.” See also Larimore & Sanford, *Postfertilization Effects of Oral Contraceptives and Their Relationship to Informed Consent*, 9 *ARCH FAM MED.* 126 (2000). Citing the Food and Drug Administration “approved product information” for oral contraceptives in the Physician’s Desk Reference, “Although the primary mechanism of action is inhibition of ovulation, other alterations include changes in the cervical mucus, which increase the difficulty of sperm entry into the uterus, and changes in the endometrium, which reduce the likelihood of implantation.”

¹³ For an overview of the “changed” definition of pregnancy, see Christopher Gacek, *Conceiving Pregnancy: U.S. Medical Dictionaries and Their Definitions of Conception and Pregnancy*, *FRC*

Though “indicated” for contraceptive use, mandated coverage for *ella* opens the door to off-label intended-abortion usage of the drug being funded by all health insurance plans. This runs directly contrary to Senator Mikulski’s assurance that “nor would abortion coverage be mandated in any way...”

Significantly, *ella* was approved by the FDA several months after the Affordable Care Act was enacted and, therefore, its inclusion in the preventive services mandate was not contemplated by Congress, even if other methods of “contraception” were. While forced coverage of contraceptives in private plans is an entirely new and unprecedented concept, in the case of *ella*, a new type of “contraceptive” drug, there is not precedent for its inclusion even in government healthcare programs. Only approved by the FDA in August 2010, there can be no reliance argument made on a history of taxpayer-funding for the abortion-inducing drug *ella* through government programs that cover other contraceptives.

c. The HRSA guidelines came from the advice of an ideologically-driven Institute of Medicine panel.

The Institute of Medicine (IOM), tasked with advising HRSA on what should be included in the preventive services mandate, had an abortion-advocacy bias in its panel membership as well as its invited presenters.

Dissenting from the IOM recommendation, committee member Dr. Anthony Lo Sasso criticized the committee’s lack of transparency and creation of an advocacy-based recommendation,

The committee process for evaluation of the evidence lacked transparency and was largely subject to the preferences of the committee’s composition. Troublingly, the process tended to result in a mix of objective and subjective determinations filtered through a lens of advocacy.¹⁴

INSIGHT PAPER (April 2009), available at <http://www.frc.org/life--bioethics> (last visited Sept. 1, 2011).

¹⁴ COMMITTEE ON PREVENTIVE SERVICES FOR WOMEN; INSTITUTE OF MEDICINE, CLINICAL PREVENTIVE SERVICES FOR WOMEN: CLOSING THE GAPS 207 (2011) available at http://www.nap.edu/catalog.php?record_id=13181 (last visited Aug. 1, 2011).

Several members of the IOM panel have direct ties to Planned Parenthood, the nation's largest abortion provider,¹⁵ which stands to gain financially from the IOM recommendation, as well as other openly pro-abortion organizations.¹⁶

A look at the organizations invited to present at the IOM's three public meetings on the preventive services mandate underscore its advocacy-based bias.¹⁷

Notably, at the first meeting, groups invited to speak on "women's issues" included the nation's largest abortion provider, Planned Parenthood. Planned Parenthood, as a distributor of "contraceptives," stands to gain tremendously if insurance plans are required to cover contraceptives without co-pay, a financial stake which was never disclosed as a conflict of interest.

¹⁵ According to her biography, Dr. Paula Johnson "served for many years on the board of Planned Parenthood League of Massachusetts and chaired the board from 1997-1998." See <http://www.bphc.org/boardofhealth/boardmembers/Pages/Home.aspx> (last visited Sept. 27, 2011); Dr. Magda Peck served as chair and vice-chair of the Board of Directors Planned Parenthood of Nebraska Council Bluffs (now Planned Parenthood of the Heartland) from 2006-2009. See http://www4.uwm.edu/secu/news_events/sph-dean/Peck-cv.pdf (last visited Sept. 27, 2011); Dr. Carol Weisman served as a member of the Affiliate Medical Committee of Planned Parenthood of Maryland from 1993-1997 and was a member of the Board of Directors of Planned Parenthood of Maryland from 1978-1984. See http://www.pennstatehershey.org/c/document_library/get_file?folderId=229089&name=DLFE-25907.pdf (last visited Sept. 27, 2011).

¹⁶ Dr. Francisco Garcia has worked with the International Planned Parenthood Federation See [http://orwh.od.nih.gov/about/Garcia%20\(updated%202-18-10\)--edited%20clean%20copy.pdf](http://orwh.od.nih.gov/about/Garcia%20(updated%202-18-10)--edited%20clean%20copy.pdf) (last visited Sept. 27, 2011); Dr. Paula Johnson serves on the board of the Center for Reproductive Rights, an organization which seeks to expand abortion access. See <http://www.bphc.org/boardofhealth/boardmembers/Pages/Home.aspx> (last visited Sept. 27, 2011); Dr. Claire Brindis is a co-founder of the Bixby Center for Global and Reproductive Health. The Bixby Center provides abortion training and runs initiatives designed to increase and expand abortion services. See <http://bixbycenter.ucsf.edu/research/abortion.html> (last visited Sept. 27, 2011). Dr. Brindis also chaired the Population, Family Planning and Reproductive Health Section (PRSH) of the American Public Health Association. The PRSH has a "task force" dedicated to abortion. See <http://www.apha.org/membergroups/sections/aphasections/population/benefits/taskforces.htm> (last visited Sept. 27, 2011); Dr. Angela Diaz has served as a Board Member for the Physicians for Reproductive Choice and Health. See <http://www.prch.org/about-board-directors> (last visited Sept. 27, 2011); and Dr. Alina Salganicoff has worked as a trainer and counselor for CHOICE, "a Philadelphia-based reproductive health care advocacy organization." See <http://www.kff.org/womenshealth/upload/Speaker-Biographies-Women-and-Health-Care-A-National-Profile.pdf> (last visited Sept. 27, 2011).

¹⁷ The IOM meeting information and agendas are available at <http://iom.edu/Activities/Women/PreventiveServicesWomen.aspx> (last visited Sept. 27, 2011).

Other invited presenters included the National Women's Law Center which states on its website, "We're working to ensure that women have access to abortion care by protecting and advancing this fundamental right."¹⁸ The second meeting included a presentation by a former official affiliate of Planned Parenthood, the Guttmacher Institute, whose "Guiding Principles" include working to "protect, expand and equalize access to information, services and rights that will enable women and men to ... exercise the right to choose abortion."¹⁹

Thus, it is unsurprising with an ideologically-stacked deck, that nearly every invited presenter urged the inclusion of *all FDA-approved contraceptives* in the mandate, without addressing any conscience concerns for Americans who oppose drugs and devices with life-ending mechanisms of action.

Further, the IOM's own Report acknowledged that the panel would have considered abortion *per se* as a "preventive service" had it not been otherwise constrained by the Affordable Care Act, "Finally, despite the potential health and well-being benefits to some women, abortion services were considered to be outside of the project's scope, given the restrictions contained in the ACA."²⁰

2. HHS' proffered conscience "accommodation" for a narrowly defined set of "religious employers" is inadequate.

The HHS regulation's proposed exemption fails to protect the serious and legitimate conscience concerns of many Americans. Instead, it disrupts the conscience protections contained in the laws of several states. The narrowly defined "accommodation" has no precedent in federal law; rather, a mandate including sterilization and abortion-inducing drugs violates the principles of long-standing federal laws protecting conscience rights.

a. The conscience exemption adopted by HHS fails to protect the conscience of many Americans

¹⁸ National Women's Law Center, *Our Issues, Abortion*, available at <http://www.nwlc.org/our-issues/health-care-%2526-reproductive-rights/abortion> (last visited Sept. 27, 2011).

¹⁹ Guttmacher Institute, *Mission*, available at <http://www.guttmacher.org/about/mission.html> (last visited Sept. 27, 2011).

²⁰ *Clinical Preventive Services for Women: Closing the Gaps*, INSTITUTE OF MEDICINE (July 19, 2011) at 21.

HHS has suggested a limited exception to the HRSA mandate, exempting a narrowly defined category of “religious employers.” However, by adopting such a narrow definition, most religiously-affiliated schools, hospitals, and charitable organizations would not be included in the exception’s protection. Moreover, non-religiously affiliated institutions – whose pro-life consciences are nonetheless violated by the mandate – are unquestionably left unprotected by the limited conscience protection.

b. The guidelines and regulation issued by HRSA and HHS disrupt duly enacted state laws protecting the conscience of healthcare payers.

Mandated coverage for contraceptives is unprecedented in nearly half the states. Even those states that have adopted so-called “contraceptive equity” laws generally only apply their requirement to insurance plans that offer prescription coverage. (Therefore allowing an employer the option, albeit a difficult choice, to drop prescription coverage altogether.) In addition, multiple states explicitly exclude certain specific FDA-labeled “contraceptives” from its mandate. Moreover, many states with religious employer exemptions adopt a more expansive definition than that provided for by the HHS regulation. Thus, the guidelines and regulation issued by the HRSA and HHS extend beyond any coercive measure enacted by the states. Further, the mandate stands in direct opposition to the duly enacted law of Mississippi which protects the conscience rights of healthcare payers. Thus, the HRSA mandate and narrow HHS “accommodation” supplants the reasoned judgment of the states with an ideologically-driven coercive measure.

The state of Mississippi has chosen to statutorily protect the conscience rights of its healthcare payers. The Mississippi law is comprehensive, and its right to decline to pay applies to any healthcare service that violates the payer’s conscience, “A health-care payer has the right to decline to pay, and no health-care payer shall be required to pay for or arrange for the payment of a health-care service that violates its conscience.”²¹ The mandate imposed by HRSA stands in direct opposition to Mississippi’s duly enacted law.

HHS is correct that the vast majority of states that have enacted contraceptive coverage laws contain an exemption for religious employers. However, many of these states define “religious employer” more broadly than HHS, and thus the mandate and regulations would trump their state protections as well. For example,

²¹ Miss. Code Ann. § 41-107-9 (2004).

Nevada law exempts insurers “affiliated with a religious organization,”²² while Missouri exempts *anyone* (not limited to religious employers) with a “moral, ethical, or religious” conscientious objection²³ and *any* health carrier “owned, operated, or controlled ... by an entity that is operated pursuant to moral, ethical or religious tenets...”²⁴ Missouri’s reasoned judgment to protect the conscience rights all its citizens would be eviscerated by the HHS rule.

Moreover, in the states that have adopted the narrow definition of religious employer proposed by HHS, their contraceptive mandates only apply to plans that offer prescription coverage. That means that employers still have the choice (admittedly a tough decision) to not offer prescription coverage. In contrast, the HRSA guidelines apply to nearly *all* insurance plans and the Affordable Care Act does not offer many organizations and individuals (without a penalty) a similar escape from its coercive measure. Even currently “grandfathered” plans will be subjected to the mandate if any number of changes is made to their plans.²⁵

In addition, many states do not require coverage for *all* FDA approved contraceptives and multiple states have explicitly chosen to reject certain so-called “contraceptives” from their mandates. For example, Arkansas clearly excludes from its mandate so-called “emergency contraception”: “Nothing contained in this subchapter shall be construed to require any insurance company to provide coverage for an abortion, an abortifacient, **or any United States Food and Drug Administration-approved emergency contraception.**”²⁶ North Carolina likewise excludes emergency contraception,²⁷ while Texas’ law excludes “abortifacients or any other drug or device that terminates a pregnancy.”

Other state laws clarify that their mandates are not to include abortion-inducing drugs. Georgia law, for example, states, “Likewise, nothing contained in this Code section shall be construed to require any insurance company to provide coverage

²² Nev. Rev. Stat. § 689A.047 (1999).

²³ Mo. Rev. Stat. § 376.1199 (2001).

²⁴ *Id.*

²⁵ See <http://www.ncsl.org/documents/health/GrandfatheredPlans.pdf>. (last visited Sept. 27, 2011). It is estimated that anywhere from 20 to 51 percent of small employer plans and 23 to 66 percent of large employer plans will retain their “grandfather” status by 2013. See http://www.healthreform.gov/newsroom/keeping_the_health_plan_you_have.html.

²⁶ Ark. Stat. Ann. §23-79-1103-1104 (2005).

²⁷ N.C. Gen. Stat. § 58-3-178 (1999). The law excludes “The prescription drug marketed under the name “Preven” or any “equivalent drug product” as defined in G.S. 90-85.27(1).”

for abortion.”²⁸ Maine’s law states that the mandate “may not apply to prescriptions designed to terminate a pregnancy.”²⁹ Rhode Island’s law includes, “[p]rovided, that nothing in this subsection shall be deemed to mandate or require coverage for the prescription drug RU 486.”³⁰ Keeping in mind that these laws, explicitly excluding the abortion drug RU-486, pre-date the approval of a substantially similar drug, *ella*, the HRSA/HHS mandated coverage preempt the principles, if not the letter, of these laws.

In addition, while the HRSA guidelines require inclusion of sterilization as a covered service, the Illinois’ contraceptive mandate states, “Nothing in this Section shall be construed to require an insurance company to cover services related to permanent sterilization that requires a surgical procedure.”³¹

Contrary to the HHS regulation’s insinuation that its “accommodation” draws it in line with the majority of states, the HRSA and HHS guidelines and regulation are a nation-wide evisceration of existing state laws.

a. A mandate including sterilization and abortion-inducing drugs violates the principles of long-standing federal laws protecting conscience rights.

The Affordable Care Act, states explicitly that “Nothing in this Act shall be construed to have any effect on Federal laws regarding – (i) conscience protection...”³² However, the mandate and regulation issued through HRSA and HHS violate the principles of long-standing federal laws that provide broad conscience protections.

Congress first addressed the issue of conscience protections just weeks after the U.S. Supreme Court decision in the *Roe v. Wade* case.³³ In 1973, Congress passed the first of the Church Amendments (named for its sponsor, Senator Frank Church).³⁴ The Amendment provides that the receipt of funding through three federal programs cannot be used as a basis to compel a hospital or individual to

²⁸ Ga. Code § 33-24-59.6 (1999).

²⁹ Me. Rev. Stat. Ann. Tit. 24 §2332-J (1999).

³⁰ R.I. Gen. Laws § 27-18-57 (2000).

³¹ Ill. Rev. Stat. ch. 215 § 5/356z.4 (2003).

³² ACA §1303(c)(2)(A)(i).

³³ 410 U.S. 113 (1973).

³⁴ 42 U.S.C. 3001-7.

participate in an abortion or sterilization procedure to which the hospital or individual has a moral or religious objection.

In addition, §§ c(2) and (d) of the Church Amendment provide broad protection ensuring that no “individual shall be required to perform or assist in the performance of any part of a health service program or research activity,” funded in whole or in part by the federal government if doing so “would be contrary to his religious beliefs or moral convictions.” Thus, the protections of the Church Amendment are broad and are not limited to abortion and sterilization.

Taken together, the original and subsequent Church Amendments protect healthcare providers from discrimination by recipients of HHS funds on the basis of their objection, because of religious belief or moral conviction, to performing or participating in *any* lawful health service or research activity.

In addition, the Hyde-Weldon Amendment, first enacted in 2005, provides that no federal, state, or local government agency or program that receives funds in the Labor/Health and Human Services appropriations bill may discriminate against a healthcare provider because the provider refuses to provide, pay for, provide coverage of, or refer for abortion.³⁵

In contrast to the principles of these federal laws which recognize a right not to be coerced into participating in abortion, sterilization, and other services “contrary to his religious or moral convictions,” the HRSA mandate leaves most Americans no option but to be on an insurance plan that covers the abortion-inducing drug *ella*, sterilization, and other “contraceptive” items and services to which he or she may have a sincerely held ethical, moral, or religious objection. The HRSA mandate is not a question of taxpayer-funding, but applies to all health insurance plans.

Conclusion

On September 9, 2009, President Obama addressed a joint session of Congress to outline his vision for a healthcare bill, and to clear up any “misunderstandings” about existing proposals.³⁶ Of particular note the President asserted, “And one

³⁵ Consolidated Appropriations Act 2008, Pub. L. No. 110-161, §508(d), 121 Stat. 1844, 2209 (2007).

³⁶ President Obama’s address in its entirety, President Barack Obama, *Remarks by the President to a Joint Session of Congress on Health Care*, September 9, 2009, available at www.whitehouse.gov/the_press_office/Remarks-by-the-President-to-a-Joint-Session-of-Congress-on-Health-Care/.

more misunderstanding I want to clear up—under our plan, no federal dollars will be used to fund abortions, and federal conscience laws will remain in place.”³⁷

Unfortunately, the HRSA guidelines and HHS regulation concerning preventive services fly in the face of the President’s assurance, as well as the very words of the Affordable Care Act and its legislative history.

It is not a tiny minority that stands in opposition to the HRSA mandate. In fact, more Americans oppose the mandate than support it. According to a Rasmussen poll, 46 percent oppose forcing “contraceptive” coverage, while only 39 percent approve.³⁸ Nor is this an issue of women versus men. Women’s opinion, according to the Rasmussen poll, was nearly evenly split. Only 40 percent of women approve, while 42 percent of women oppose the mandate. Even these numbers fail to tell the entire story, considering Rasmussen did not mention that abortion-inducing drugs and devices, such as *ella*, are included in mandate.³⁹

In accord with the language and history of the Affordable Care Act and the weight of public opinion, Americans United for Life implores HHS to repeal the HRSA guidelines mandating coverage for all FDA approved contraceptives and sterilization.

The damage done by the mandate will be hard to counteract once the insurance market stops accommodating conscience rights. Thus, immediate action on the part of HHS is necessary to address the inappropriate HRSA mandate.

Sincerely,

/s/ Anna Franzonello
Staff Counsel
Americans United for Life

³⁷*Id.*

³⁸See 39% Say Health Insurance Companies Should Be Required to Cover Contraceptives, RASMUSSEN REPORTS, Aug. 4, 2011 available at http://www.rasmussenreports.com/public_content/politics/current_events/healthcare/august_2011/39_say_health_insurance_companies_should_be_required_to_cover_contraceptives (last visited Sept. 27, 2011).

³⁹*Id.* Rather, the question posed was general, “Should health insurance companies be required by law to cover all government-approved contraceptives for women, without co-payments or other charges to the patient?”